UNIVERSIDAD COMPLUTENSE DE MADRID

Facultad de Veterinaria

TESIS DOCTORAL

Feline degenerative joint disease: studies of prevalence, etiology and diagnosis

Enfermedad degenerativa articular felina: estudios de prevalencia, etiología y diagnóstico

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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Madrid, 2014

Universidad Complutense de Madrid
Facultad de Veterinaria

Feline Degenerative Joint Disease: Studies of prevalence, etiology and diagnosis

by

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Thesis submitted at the
Complutense University of Madrid

Thesis Director
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2014

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Memoria para optar al grado de doctor
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Director de Tesis
Dr. B Duncan X Lascelles

2014

Dr Duncan X. Lascelles, Profesor Titular de Cirugía de Pequeños Animales en la Facultad de Veterinaria de la Universidad de Carolina del Norte,

CERTIFICA:

Que la Tesis Doctoral titulada **"Enfermedad degenerativa articular felina: estudios de prevalencia, etiología y diagnostico"**, ha sido realizada bajo su dirección y supervisión por Dª Milagros Freire González.

Revisado el presente trabajo, considera que tiene la debida calidad para su presentación y defensa.

Dr. Duncan X Lascelles

Raleigh, 7th April 2014

INDICE

Página

AGRADECIMIENTOS

A veces las cosas son inexplicablemente imposibles hasta que alguien altruistamente te tiende la mano que hace que todo el esfuerzo y trabajo realizado se materialice y cobre sentido. No agradezco a los que no me pusieron impedimentos sino a los que creyeron que este trabajo era posible y me ayudaron a que se hiciera realidad.

Gracias, Javier Benito de la Víbora.

Gracias, Ignacio Álvarez Gómez de Segura.

Dedicado a Miriam Martín García.

RESUMEN

La tesis detallada en este documento está dividida en cuatro secciones que corresponden con artículos publicados en diferentes revistas de difusión veterinaria. En conjunto estos estudios tienen como objetivo general profundizar en el mejor conocimiento de la patología articular en gatos domésticos, en concreto, avanzar en los conocimientos acerca de la prevalencia, etiología y diagnóstico de esta enfermedad.

El primer estudio incluido en esta tesis se diseñó para determinar la prevalencia de la presencia de signos radiológicos indicativos de enfermedad articular degenerativa en una población de gatos seleccionados aleatoriamente. El estudio fue diseñado como un estudio prospectivo observacional. Los animales incluidos fueron 100 gatos domésticos con dueño, seleccionados de la base de datos de una clínica veterinaria felina local, y fueron equitativamente distribuidos en cuatro grupos de edades (0-5, 5-10, 10-15 y de 15 a 20 años de edad). Estos animales fueron seleccionados aleatoriamente de la base de datos (independientemente de su estado de salud en el momento de la realización del estudio) y durante su visita al hospital fueron sedados para realizar el estudio radiológico de todas las articulaciones apendiculares y la columna vertebral. La información generada se analizó por medio de un test de regresión Quasi-Poisson para investigar la relación entre los datos demográficos de la población, los valores de la analítica sanguínea (hematológicos y bioquímicos) análisis de orina y la severidad de la enfermedad degenerativa articular presente. Los resultados más destacables fueron que la mayoría de los gatos (92%) presentaron evidencia radiológica de enfermedad articular degenerativa; el 91% presentaban al menos una articulación apendicular afectada de enfermedad articular degenerativa y el 55% presentaba una o más regiones de la columna vertebral con signos radiológicos indicativos de esta enfermedad. Las articulaciones apendiculares más

frecuentemente afectadas de enfermedad articular degenerativa, ordenadas de mayor a menor frecuencia, fueron la cadera, rodilla, tarso y codo. El segmento torácico de la columna vertebral fue el que más frecuentemente presentaba signos radiológicos indicativos de degeneración articular. Muchas variables presentaron una asociación significativa con la presencia de enfermedad degenerativa articular, pero cuando estas variables fueron agrupadas para el análisis, la única asociación estadísticamente significativa encontrada fue entre edad y enfermedad degenerativa articular ($P < 0,0001$). Por cada año de aumento de edad de los gatos, el valor total del grado de enfermedad articular degenerativa esperado aumenta en un porcentaje estimado en 13,6% (95% intervalo de confianza: 10,6%, 16,8%). Este estudio permitió por primera vez de una forma prospectiva, con un número elevado de animales y realizando radiografías de todas las articulaciones apendiculares y segmentos vertebrales, establecer que la presencia de signos radiológicos indicativos de enfermedad articular degenerativa tiene una prevalencia muy alta en gatos domésticos, incluso en animales jóvenes, y está fuertemente asociada con la edad del animal. Aún son necesarios futuros estudios para determinar las consecuencias clínicas de esta enfermedad en gatos domésticos.

Gracias a estudios de prevalencia como el mencionado arriba y otros publicados recientemente, la enfermedad articular degenerativa ha sido descrita como una de las afectaciones más comunes en los gatos domésticos pero durante mucho tiempo no ha estado claro cuáles son los signos radiológicos indicativos de esta enfermedad en la especie felina, o si estos signos radiológicos son diferentes a otras especies en las que si están bien descritos, por ejemplo el perro. El segundo estudio incluido en este trabajo consistió en describir como los signos radiológicos considerados indicativos de la presencia de enfermedad articular

degenerativa se relacionan con la degeneración del cartílago articular de las articulaciones apendiculares en esta especie. Treinta gatos adultos, eutanasiados por causas independientes a la realización de este estudio, fueron evaluados. Signos radiológicos indicativos de la presencia de enfermedad articular degenerativa se evaluaron en radiografías ortogonales de las articulaciones del codo, tarso, rodilla y cadera. Estas mismas articulaciones se inspeccionaron visualmente postmortem con el objetivo de detectar la presencia de lesiones indicativas de enfermedad degenerativa articular, y determinar el grado de lesión del cartílago articular usando la escala "Grado de Daño Articular Total" (*Total Cartilage Damage Score*). Los resultados más significativos de este estudio fueron que evaluando todas las articulaciones en conjunto hay una correlación que, aunque significativa, es baja entre el grado de daño articular observado durante la inspección visual de las articulaciones y la severidad de osteofitos y mineralizaciones de los tejidos blandos asociados con tejidos articulares detectados radiográficamente, así como con el grado de enfermedad articular degenerativa asignado a las radiografías de cada articulación subjetivamente (*subjective radiographic DJD score*). Evaluando cada articulación por separado, la mayoría de las correlaciones estudiadas fueron estadísticamente significativas, sin embargo el grado de correlación fue superior a 0,4 (moderado) únicamente en las articulaciones del codo y la cadera para las correlaciones entre la presencia de osteofitos en las radiografías y el grado subjetivo radiológico de enfermedad degenerativa articular con el daño del cartílago articular detectado macroscópicamente. Las articulaciones en las que es más probable encontrar daño del cartílago articular sin presentar ningún signo radiológico indicativo de enfermedad degenerativa articular son la rodilla (71% de las rodillas radiológicamente normales presentaron daño del cartílago articular), seguido de la articulación de la cadera (57%), el codo (57%) y la articulación del tarso (46%). Los resultados de este estudio determinan que los signos radiológicos presentes

en las articulaciones apendiculares en gatos domésticos no se correlacionan con la presencia de daño en el cartílago articular, el número de articulaciones con daño articular que no presentaron ningún signo radiológico de enfermedad articular degenerativa es alto, y otras modalidades de diagnóstico por imagen deberían ser consideradas como opciones para el diagnóstico de la enfermedad articular degenerativa felina.

La evaluación de las radiografías durante el desarrollo de los dos estudios anteriores, puso de manifiesto la presencia de mineralizaciones en la articulación de la rodilla en un número importante de animales y esto propició el planteamiento de un estudio en el que los objetivos principales fueron determinar la prevalencia de mineralizaciones del menisco detectables radiográficamente en gatos domésticos y evaluar la asociación entre la mineralización del menisco y la presencia de enfermedad articular degenerativa en la articulación de la rodilla. El estudio fue diseñado como un estudio observacional prospectivo en el que se evaluaron 100 gatos con dueño y 30 gatos adultos que fueron eutanasiados por motivos no relacionados con este estudio. Los 100 gatos con dueño evaluados, fueron seleccionados aleatoriamente de una base de datos perteneciente a una clínica veterinaria felina local, y la información recopilada de estos animales se utilizó para determinar la prevalencia de la mineralización del menisco. Las articulaciones de la rodilla de los gatos eutanasiados fueron utilizadas para evaluar la relación entre la presencia y el tamaño de la mineralización del menisco (usando radiografías de gran resolución), la presencia de signos radiológicos indicativos de enfermedad degenerativa articular y la presencia de lesiones en el cartílago articular. Los meniscos extraídos de estas articulaciones fueron procesados y evaluados histológicamente. Los resultados más significativos de este estudio fueron que el 46% de los 100 gatos evaluados tenían evidencia radiológica de

mineralización del menisco en una o las dos rodillas. El grado de dolor detectado en el examen ortopédico en las rodillas no presentó diferencias significativas entre articulaciones con y sin mineralización del menisco (P = 0,38). Treinta y cuatro de las 57 rodillas evaluadas postmortem presentaban mineralización del menisco, y esta mineralización estaba localizada en el cuerno craneal del menisco medial en todos los casos. El porcentaje del área total del menisco que presentaba mineralización se correlacionó significativamente con el grado de lesión del cartílago articular del cóndilo medial del fémur (r^2 = 0,6; P < 0,0001) y del cóndilo medial de la tibia (r^2 = 0,5; P < 0,0001) así como con el grado de lesión global del cartílago articular de la articulación (r^2 = 0,36; P < 0,0001) y la severidad de los signos radiológicos de enfermedad articular degenerativa presentes (r^2 = 0,8; P < 0,0001). En conclusión, la mineralización del menisco es una condición presente comúnmente en gatos domésticos y parece indicar la presencia de enfermedad degenerativa articular en el compartimento medial de la articulación de la rodilla en esta especie.

Finalmente debido a que la articulación del codo en los gatos domésticos ha sido descrita en numerosos estudios como una de las articulaciones apendiculares más comúnmente y severamente afectadas por enfermedad articular degenerativa, un cuarto estudio fue diseñado para evaluar las lesiones macroscópicas e histológicas en la articulación del codo en 30 gatos adultos, inmediatamente después de la eutanasia. Lesiones macroscópicas indicativas de enfermedad degenerativa articular se encontraron en 22 de los 30 gatos evaluados (39 codos) (73,33% de los gatos; 65% de las articulaciones estudiadas) y las lesiones del cartílago variaron desde ligera erosión superficial a destrucción completa del cartílago articular con exposición del hueso subcondral. La distribución de las lesiones en el cartílago se corresponde con la presencia

de enfermedad degenerativa del compartimento medial de la articulación (las lesiones más severas se localizaron en el proceso coronoideo medial de la ulna y en el epicóndilo medial del húmero). En 10 codos se encontraron fragmentos osteocondrales intra-articulares, en algunos casos libres en el espacio articular y en otros adheridos a la membrana sinovial. En general el grado de inflamación de la membrana sinovial fue solo ligero incluso en casos con lesiones severas del cartílago articular, y presentó una correlación baja con el grado de destrucción del cartílago articular detectado macroscópicamente. No se encontró evidencia macroscópica o histológica de la presencia de fragmentación del proceso coronoideo medial de la ulna en ningún caso, ni siquiera en aquellos que presentaron fragmentos osteocondrales intra-articulares. Las lesiones observadas en los animales estudiados probablemente representan osteocondromatosis sinovial secundaria a la presencia de enfermedad articular degenerativa. La patogénesis de la compartimentalización medial de la enfermedad degenerativa articular en los gatos estudiados no ha podido ser determinada pero no parece estar relacionada con la presencia de fragmentación del proceso coronoideo medial u osteocondritis disecante del húmero.

Con estos resultados, creemos que los estudios detallados en esta tesis han contribuido a mejorar el conocimiento de las características radiológicas y patológicas de la enfermedad degenerativa articular felina. Algunos de los signos radiológicos que se pueden encontrar comúnmente en esta especie, como la mineralización del menisco de la articulación de la rodilla han sido finalmente detallados y han sido asociados con un daño severo del cartílago articular. Los estudios de etiología realizados han permitido determinar, por ejemplo, que algunas causas muy bien descritas y conocidas en otras especies domesticas causantes de enfermedad degenerativa en el codo, como es el caso de la displasia de codo en la especie canina, hayan sido

descartadas como causas de enfermedad degenerativa en esta misma articulación en gatos domésticos. Muchas preguntas están aún sin responder y futuros estudios son necesarios para elucidar más aspectos relacionados con la etiología y la significación clínica de esta enfermedad en los gatos domésticos.

Summary

The detailed herein thesis is divided into four sections that correspond to manuscripts published in different journals of veterinary diffusion. Together these studies' general aim is to deepen the knowledge of joint disease in domestic cats, in particular, improve what we know about the prevalence, etiology, and diagnosis of this disease.

The first study described this thesis was designed to determine the prevalence of radiographic signs of degenerative joint disease (DJD) in a randomly selected sample of domestic cats. The study was designed as a prospective observational study. One hundred client-owned cats from a single feline only veterinary practice and equally distributed across 4 age groups (0-5, 5-10, 10-15, and 15-20 years old) were randomly selected (regardless of health status) and sedated for orthogonal radiographic projections of all joints and the spine. Quasi-Poisson regression analysis was used to investigate the relationship between patient demographics, blood biochemistry, hematologic and urine analysis variables, and DJD severity. The most significant results were that the majority of cats (92%) had radiographic evidence of DJD; 91% of animals had at least one site of appendicular DJD and 55% had one or more sites of the axial column affected with DJD. Affected joints in descending order of frequency were hip, stifle, tarsus and elbow. The thoracic segment of the spine was more frequently affected than the lumbosacral segment. Although many variables were significantly associated with DJD, when variables were combined, only the association between age and DJD was significant ($P < .0001$). For each 1-year increase in cat age, the expected total DJD score increases by an estimated 13.6% (95% confidence interval: 10.6%, 16.8%). This study allowed for the first time in a prospective manner and with a high number of animals, to determine that radiographically visible DJD is very common in domesticated cats, even in young animals and that is strongly

associated with age however it is necessary further investigation to determine the clinical consequences of this disease.

As a consequence of studies of prevalence as the one described above and others more recently published, degenerative joint disease is now described as one of the most common conditions affecting domesticated cats; however for many years, it was not clear which were the radiographic signs indicative of this disease in feline species or if these radiographic signs were different to other species in which they are accurately described, for example in canine species. The second study included in this thesis was designed to describe the relationship between the radiographic signs considered indicative of the presence of degenerative joint disease and the macroscopic cartilage degeneration in appendicular joints in cats. Thirty adult cats euthanized for reasons unrelated to this study were evaluated. Orthogonal digital radiographs of the elbow, tarsus, stifle and coxofemoral joints were evaluated for the presence of DJD. The same joints were dissected for visual inspection of changes indicative of DJD and macroscopic cartilage damage was graded using a Total Cartilage Damage Score. The most significant results were that when considering all joints, there was statistically significant fair correlation between cartilage damage and the presence of osteophytes and joint-associated mineralizations, and the subjective radiographic DJD score. Most correlations were statistically significant when looking at the different joints individually, but only the correlation between the presence of osteophytes and the subjective radiographic DJD score with the presence of cartilage damage in the elbow and coxofemoral joints had a value above 0.4 (moderate correlation). The joints most likely to have cartilage damage without radiographic evidence of DJD are the stifle (71% of radiographically normal joints), followed by the coxofemoral joint (57%), elbow (57%), and tarsal joint (46%).

The results of this study support that radiographic signs of appendicular joints do not relate well with articular cartilage degeneration, and that other modalities should be evaluated to aid in making a diagnosis of feline DJD.

The evaluation of radiographs of appendicular joints of domestic cats during the development of the two previous studies, revealed the presence of mineralizations in the stifle joint in a large number of animals and this encouraged the development of the next study. The main objectives were to determine the prevalence of radiographically detectable meniscal mineralization in domestic cats and assessment of the association between meniscal mineralization and the presence of degenerative joint disease in the stifle joint in this species. The study was designed as a prospective study. Thirty adult cats euthanized for reasons unrelated to this study and 100 client-owned domestic cats were evaluated. The client-owned cats were randomly selected from a database of a feline-only single practice and the information from these animals was used to determine the prevalence of radiographic signs indicative of meniscal mineralization. Stifle joints from feline cadavers were used to evaluate the relationship between the presence and size of meniscal mineralization (using high-resolution X-ray), radiographic DJD, and cartilage damage. Menisci were also harvested and processed for histological evaluation. The most significant results of this study were that 46% of the client-owned cats had meniscal mineralization detected in 1 or both stifles. Pain scores were not significantly different between stifle with meniscal mineralization and those with no radiographic pathology ($P = .38$). Thirty-four of 57 cadaver stifles had meniscal mineralization, which was always located in the cranial horn of the medial meniscus. Percentage mineralization of the menisci was significantly correlated with the cartilage damage score of the medial femoral ($r^2 = 0.6$; $P < .0001$) and tibial

($r^2 = 0.5$; $P < .0001$) condyles as well as with the total joint cartilage damage score ($r^2 = 0.36$; $P < .0001$) and DJD score ($r^2 = 0.8$; $P < .0001$). In conclusion, meniscal mineralization is a common condition in domestic cats and seems to indicate medial compartment DJD of the stifle joint. The clinical significance of this condition in feline species is uncertain and further work is needed to determine if the meniscal mineralization is a cause or a consequence of joint degeneration.

Finally because the elbow joint in domestic cats has been described in numerous studies as one of the appendicular joints most commonly and severely affected by DJD, a fourth study was designed to evaluate the pathologic changes present in the elbow joints of 30 adult cats immediately following euthanasia. All the joints were carefully opened for macroscopic evaluation of the articular cartilage and samples of joint capsule and articular cartilage of ulna, humerus and radius were processed for histological evaluation. Macroscopic evidence of degenerative joint disease was found in 22 of 30 cats (39 elbow joints), (73.33% cats; 65% elbow joints), and macroscopic cartilage erosion ranged from mild fibrillation to complete ulceration of the hyaline cartilage with exposure of the subchondral bone. Distribution of the lesions in the cartilage indicated the presence of medial compartment joint disease (with the most severe lesions located in the medial coronoid process of the ulna and medial humeral epicondyle). Synovitis scores were mild overall and correlated only weakly with macroscopic cartilage damage. Intra-articular osteochondral fragments either free or attached to the synovium were found in 10 joints. Macroscopic or histologic evidence of fragmented coronoid process was not found even in those cases with intra-articular osteochondral fragments. Lesions observed in these animals are most consistent with synovial osteochondromatosis secondary to degenerative joint disease. The pathogenesis for the medial compartmentalization of these lesions has not been

established, but a fragmented medial coronoid process or *osteochondritis dissecans* does not appear to play a role.

Together these studies have contributed to improve the knowledge of radiographic, macroscopic and pathologic characteristics of joint disease in domestic cats. Some of the radiographic signs present in this species, such as mineralization of the medial meniscus of the stifle joint, have been found to be associated with a severe damage of the articular cartilage. Etiology studies conducted have allowed to determine, for example, that very well described and known causes of joint pathology in other species, such as elbow dysplasia in dogs, have been dismissed as causes of degenerative disease in the same joint in domestic cats. Many questions are still unanswered and future studies are needed to further elucidate aspects of the etiology and clinical significance of DJD in domestic cats.

Introduction

Until very recently, little was known about feline degenerative joint disease (DJD). Only a few retrospective studies were available a few years ago,[1-4] and although they stressed the high prevalence of radiographic signs of DJD in this species, there were still many unknown aspects regarding this condition in cats. Over the years, there has been much speculation on feline DJD and likely, many erroneous presumptions based on DJD in other species. It seems timely to critically review what is now known about feline DJD and to identify needed information to appropriately address this clinical entity. This work embraces different studies that were conducted to deepen the knowledge of prevalence, etiology and diagnosis of feline DJD.

Several studies have been performed to evaluate the prevalence of feline DJD. Beadman *et al* [5] undertook the first extensive radiographic evaluation of DJD of the feline axial skeleton. Since then, the studies that have been carried out suggest that the most frequent site of axial skeleton DJD is the area T7-10.[6, 7,8] The most severe lesions appear to be in the lumbar or lumbo-sacral region. The incidence of axial skeleton DJD is markedly different between the different studies, likely reflecting an increase in frequency of axial skeleton DJD with age. The available information at the time of publication of our study of the prevalence of feline DJD (publication number 1, Page x), suggested that the appendicular joints most commonly affected by DJD are the hip and elbow, followed by stifle or possibly tarsus.[6-12] Although these studies suggested a high incidence of radiographic signs indicative of appendicular and axial DJD in cats, prior to publication of the study of prevalence included in this thesis, no studies had been published that evaluate every appendicular joint and every region of the axial skeleton, in a randomly selected population of cats to ascertain the prevalence of appendicular and axial DJD in this species. For more information please refer to manuscript number 1 of this document (Lascelles BD, Henry JB 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, Wheeler S, Hansen BD, Zamprogno H, Freire M, Pease A.B. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Veterinary Surgery*. 2010;39(5):535-44).

The high prevalence of this disease generated interest in describing the clinical signs, evaluating causes and predisposing factors and measuring the pain associated with the radiographic changes. Despite this interest, for many years there was no information on how the radiographic findings of feline DJD related to actual degeneration of various joint components, such as cartilage. Seemingly, there were no studies in cats comparing the radiographic appearance of joints with histological findings. Such comparison was necessary to improve radiographic interpretation and to address the idea that feline DJD may be associated with different radiographic signs and macroscopic lesions compared with other species, as it has been previously suggested. For more information please refer to manuscript number 2 of this document (Freire M, Robertson I, Bondell HD, Brown J, Hash J, Pease AP, Lascelles BD. Radiographic evaluation of feline appendicular degenerative joint disease versus macroscopic appearance of articular cartilage. *Veterinary Radiology & Ultrasound*. 2011;52(3):239-47).

Although common causes of OA in cats have been outlined before,[13] there is little documented supporting evidence and most studies evaluating prevalence speculate on the cause of DJD. Clarke *et al* [8] indicated that about 25% of OA cases resulted from trauma, with more than 50% of cases having no obvious cause suggesting that they may have been primary OA. Hardie *et al* [9] found little evidence in medical records to indicate likely cause of DJD and postulated that observed OA/DJD was likely secondary to undetermined factors (eg. elbow dysplasia, chronic low-grade trauma, subtle malarticulation). Several authors have suggested that a large proportion of DJD in cats is primary; however there is currently no supporting evidence. It is possible that unrecognized factors, such as those that play a role in other species, may be responsible for DJD in cats. It is also possible that as yet unrecognized factors that do not play a significant role in DJD in other species, such as systemic inflammatory disease, may predispose to, or be the cause of, DJD in the cat. Documented secondary causes of DJD in cats are nutritional, hip dysplasia and noninfectious polyarthropathies and infectious arthropathies.

Of interest is the frequent bilateral occurrence of feline DJD, a characteristic of DJD caused by bilateral congenital malformations (eg. joint dysplasia, osteochondrosis), systemic factors (eg. endocrinopathy, metabolic disorders), neurogenic factors, chronic overuse or possible primary OA. Joints reported to be most commonly affected by DJD are hip and stifle[14] or shoulder and elbow[15] depending of the study and bilateral occurrence is most common in coxofemoral, carpal, elbow and stifle joints.[14] We evaluated the presence of meniscal mineralization in domestic cats as a possible cause of bilateral DJD in the stifle joint. Meniscal mineralization is a poorly understood condition that has been reported in reptiles, rodents, birds, non-domestic cats, and non-human primates.[16-19] Although described in people, it is considered a rare condition[20-27] and there have been a few case reports in dogs and domestic cats.[26, 28, 29] The cause of meniscal mineralization is unknown. It had been suggested that meniscal mineralization is a normal anatomic feature in non-domestic cats,[17] a primary vestigial anomaly in dogs and cats,[16, 29] and to occur secondary to trauma or in association with cranial cruciate ligament rupture in dogs and cats.[16, 28] At the time of publication of our study of meniscal mineralizations in domestic cats, the frequency of occurrence of this condition was unknown. It was also unknown if meniscal mineralization was associated with joint pain or lameness or if meniscal mineralization was associated with degeneration of joint tissues such as cartilage. For more information please refer to manuscript number 3 of this document (Freire M, Brown J, Robertson ID, Pease AP, Hash J, Hunter S, Simpson W, Thomson Sumrell A, Lascelles BD. Meniscal Mineralization Domestic Cats. *Veterinary Surgery*. 2010;39(5):545-52).

The elbow joint in cats has been described as one of the joints most commonly affected by DJD with an incidence of radiographic evidence of DJD in approximately 41% of the cases and bilateral disease reported in 28% of the cases.30 The elbow joint is commonly affected by DJD in dogs as well,31 but unlike cats the majority of canine patients with elbow joint DJD have known underlying predisposing factors such as fragmented medial coronoid process (FMCP) or osteochondritis dissecans (OCD). To date, these forms of elbow dysplasia have not been proven to be present in cats. One report suggested the

occurrence of elbow dysplasia (fragmented medial coronoid process) as a cause of elbow disease in a feline patient after removal of several osteochondral fragments from both elbow joints.[32] As part of the study presented in this thesis as publication number 2, we have observed similar fragments in cats with elbow DJD, in which evidence of macroscopic cartilage damage is present but with apparently intact coronoid processes of the ulna on macroscopic examination. Even though the prevalence of radiographic signs of DJD in the elbow joint in cats is high and fragmented medial coronoid process has been suggested to be present in this species, the etiology of feline elbow DJD is unknown and the presence of feline elbow dysplasia has not been confirmed. The last study included in this work was designed to report the histological characteristics of the articular surfaces, synovial membranes and intra-articular osteochondral fragments in elbow joints from cats with and without DJD and compare the findings with those reported to be present in dogs with FMCP. For more information please refer to manuscript number 4 (Freire M, Meuten D, Lascelles, BDX. Pathology of articular cartilage and synovial membrane from elbow joints with and without degenerative joint disease in domestic cats. *Veterinary Pathology*. 2014 Jan 29. [Epub ahead of print]).

OBJECTIVES

Study 1: Cross-Sectional study of the Prevalence of Radiographic Degenerative Joint disease in Domesticated Cats. *Veterinary Surgery*. 2010; 39(5):535-544.

a. Evaluate the prevalence of radiographic signs of DJD in a sample of cats selected at random from a population of domestic cats.

b. Evaluate associations between severity of radiographic DJD and patients demographics, serum biochemical profile, hematological profile and urinalysis profile variables.

Study 2: Radiographic evaluation of feline appendicular degenerative joint disease versus macroscopic appearance of articular cartilage. *Veterinary Radiology & Ultrasound*. 2011;52(3):239-47.

a. Evaluation of the sensitivity of digital and analog radiographs for detection of radiographic signs indicative of DJD in cats.

b. Evaluate the association between radiographic features of DJD and the presence of macroscopically detectable articular cartilage damage in feline appendicular joints.

Study 3: Meniscal Mineralization Domestic Cats. *Veterinary Surgery*. 2010;39(5):545-52.

a. Determine the prevalence of radiographically detectable meniscal mineralization in domestic cats.

b. Determine the association between meniscal mineralization and the presence of stifle joint DJD as indicated by cartilage damage.

Study 4: Histopathology of articular cartilage and synovial membrane from elbow joints with and without degenerative joint disease in domestic cats. *Veterinary Pathology*. 2014 Jan 29. [Epub ahead of print].

a. Evaluate the histological characteristics of the articular surfaces, synovial membranes and intra-articular osteochondral fragments in elbow joints from cats with and without DJD.

b. Compare histological findings of elbow joints of cats with DJD with those published for dogs with fragmented medial coronoid process.

c. Evaluate the association between macroscopic and histological degree of damage of articular surfaces with the degree of synovial inflammation and hyperplasia.

PUBLICATIONS

Publication 1

Lascelles BD, Henry JB 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, Wheeler S, Hansen BD, Zamprogno H, **Freire M**, Pease A.B. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Veterinary Surgery*. 2010;39(5):535-44.

Publication 2

Freire M, Robertson I, Bondell HD, Brown J, Hash J, Pease AP, Lascelles BD. Radiographic evaluation of feline appendicular degenerative joint disease versus macroscopic appearance of articular cartilage. *Veterinary Radiology & Ultrasound*. 2011;52(3):239-47.

Publication 3

Freire M, Brown J, Robertson ID, Pease AP, Hash J, Hunter S, Simpson W, Thomson Sumrell A, Lascelles BD. Meniscal Mineralization Domestic Cats. *Veterinary Surgery*. 2010;39(5):545-52.

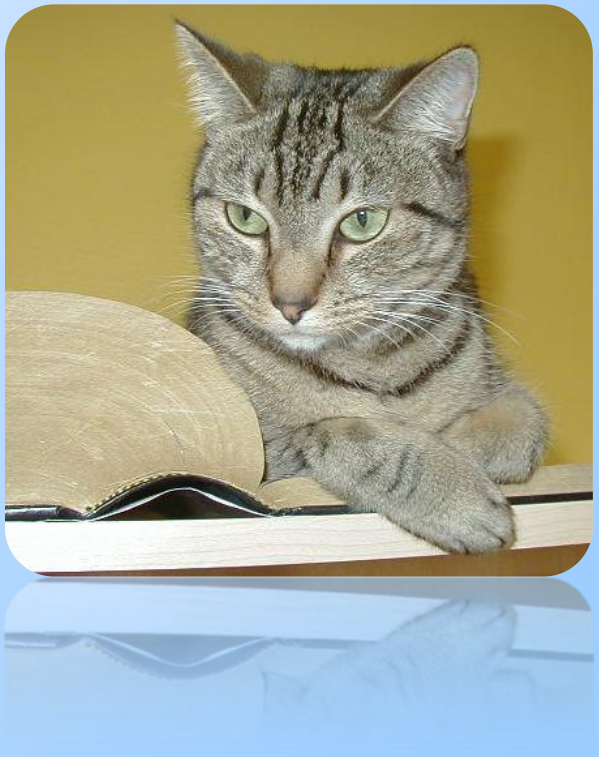
Publication 4

Freire M, Meuten D, Lascelles BD. Histopathology of articular cartilage and synovial membrane from elbow joints with and without degenerative joint disease in domestic cats. *Veterinary Pathology*. 2014 Jan 29. [Epub ahead of print].

PUBLICATION 1

Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. Lascelles BD, Henry JB 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, Wheeler S, Hansen BD, Zamprogno H, Freire M, Pease A.B. *Veterinary Surgery*. 2010;39(5):535-44.

http://www.ncbi.nlm.nih.gov/pubmed/20561321



Cross-Sectional Study of the Prevalence of Radiographic Degenerative Joint Disease in Domesticated Cats

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Submitted July 2009
Accepted November 2009

DOI:10.1111/j.1532-950X.2010.00708.x

Objective: To determine the prevalence of radiographic signs of degenerative joint disease (DJD) in a randomly selected sample of domestic cats.
Study Design: Prospective observational study.
Animals: Client-owned cats.
Methods: Cats (n = 100) from a single practice and equally distributed across 4 age groups (0–5; 5–10; 10–15, and 15–20 years old) were randomly selected (regardless of heath status) and sedated for orthogonal radiographic projections of all joints and the spine. Quasi-Poisson regression analysis was used to investigate the relationship between patient demographics, blood biochemistry, hematologic and urine analysis variables, and DJD severity.
Results: Most (92%) cats had radiographic evidence of DJD; 91% had at least 1 site of appendicular DJD and 55% had $\geq$1 site of axial column DJD. Affected joints in descending order of frequency were hip, stifle, tarsus, and elbow. The thoracic segment of the spine was more frequently affected than the lumbosacral segment. Although many variables were significantly associated with DJD, when variables were combined, only the association between age and DJD was significant ($P < .0001$). For each 1-year increase in cat age, the expected total DJD score increases by an estimated 13.6% (95% confidence interval: 10.6%, 16.8%).
Conclusion: Radiographically visible DJD is very common in domesticated cats, even in young animals and is strongly associated with age.
Clinical Relevance: DJD is a common disease of domesticated cats that requires further investigation of its associated clinical signs.

Despite recent attempts to characterize feline degenerative joint disease (DJD) by radiographic changes and associated clinical signs,[1,2] surprisingly little is known.

Beadman et al[3] reported the first extensive radiographic evaluation of DJD of the feline axial skeleton and subsequent studies[1,2,4,5] suggest that the most frequent site of axial skeletal DJD is T7-10. The most severe lesions appear to be in the lumbar or lumbosacral region. The incidence of axial skeleton DJD is markedly different between studies, likely reflecting an increase in frequency of axial skeleton DJD with age. The most commonly affected appendicular joints are the hip and elbow, followed by stifle or possibly tarsus[1,2,4–8]; however, we are unaware of studies that evaluate every joint in a randomly selected population of cats to ascertain the prevalence of DJD. Little is known about the cause of feline DJD, and it is possible it may be associated with other systemic disease, environmental, or management factors.

Our purpose was to evaluate the prevalence of radiographic signs of DJD in a sample of cats between 6 months and 20 years of age, selected at random from a population of domestic cats. Further, we evaluated associations between severity of radiographic DJD, and patient demographics, serum biochemical, hematologic, and urinalysis profile variables.

MATERIALS AND METHODS

This prospective, observational study was approved by our institutional Animal Care and Use Committee. All clients signed a consent form after being fully informed about the

study and the risks associated with participation. Using a database of 1640 cats from a single veterinary practice, a sample of 100 cats was randomly selected for study as described below. We wanted to evaluate cats across a broad range of ages while concurrently selecting cats randomly from this population. To achieve this, cats in the database were divided into 4 age groups (6 months to 5 years; 5–10 years; 10–15 years; and 15–20 years old). Cats that were exactly 5, 10, or 15 years old were assigned to the 6 months–5 years, 5–10 years, and 10–15 years groups, respectively.

Within each age group, each cat was assigned a unique number, and then the cats in each group were randomly ranked using shuffled cards. All cats were included, regardless of health status. The first 25 cats in each age group whose owners were willing to participate in the study were included. Owners were contacted in order of ranking, and were sent up to 2 recruitment letters at 1-month intervals, and then contacted by telephone. If there was no response, or they declined, the next randomly selected owner was contacted. The investigators worked diligently to persuade owners to enroll the selected cats.

Once selected, owners visited the NCSU Veterinary Teaching Hospital and each cat had a general physical examination and body condition score (BCS) performed using a 5-grade body index system (1-emaciated; 2-thin; obvious abdominal waist; 3-ideal; 4-overweight; no observable abdominal waist; 5-obese).[9] Age, weight, sex, BCS, amount of time spent indoors and outdoors, vaccination status (rabies, FeLV, FVRCP), and percentage (%) of the diet that was dry food were recorded. Hematologic and serum biochemical profile analysis, fructosamine and T4 levels, FeLV/FIV testing, and urinalysis (specimen collected by cystocentesis) were performed after completion of radiographs.

Radiographic Technique

Each cat was sedated for radiographic examination using a combination of ketamine (3–5 mg/kg), butorphanol (0.3–0.4 mg/kg), and medetomidine (10–15 μg/kg) administered intramuscularly. Doses were adjusted where it was considered clinically appropriate. Medetomidine was reversed with atipamezole administered intramuscularly (5 times the dose [μg] of medetomidine administered) after completion of the radiographic study. Cats with cardiac disease (auscultable murmurs with or without clinical signs) were sedated with a combination of buprenorphine (30 μg/kg) and acepromazine (0.03 mg/kg) intramuscularly. The lead investigator and technician (A.T.) was present for the duration of sedation of every cat, and every cat was monitored during recovery.

Orthogonal radiographs of all joints and the spine were taken using an indirect digital flat panel imaging system (Canon Medical CXDI-50G Sensor, Eklin Medical Systems, Santa Clara, CA). Radiographs were centered on the midpoint of the limb or spinal segment. Radiography continued until good quality orthogonal projections of every joint or axial segment were obtained. Quality control was performed by the lead investigator and the radiology technicians.

Radiographic Interpretation

Criteria for evaluation of radiographic signs of feline appendicular joints and axial skeleton DJD were established by 3 board-certified radiologists (I.R., J.B., A.P.) and 1 board-certified surgeon (B.D.X.L.). Additional assistance was provided by 1 author (M.F.) who had been investigating the relationship between radiographic features of feline DJD and the histologic appearance of joints. Criteria were established after detailed evaluation and discussion of radiographs taken in the same manner from a separate group of 30 cats that were being evaluated as part of a different feline DJD study. Once the criteria for evaluation of radiographic signs of DJD were defined, the radiographs were assessed by 2 of the board-certified radiologists (J.B., A.P.) and a board-certified surgeon (B.D.X.L.). Stored digital radiographs (Amicas PACS, Amicas Inc., Boston, MA) were viewed by each assessor using e-film (eFilm 3.1, Merge Healthcare, Milwaukee, MI) on 24 in. high-resolution color computer monitors (Dell, Round Rock, TX) calibrated for viewing digital radiographs.

The manus and pes were considered as 1 joint region for evaluation purposes. Other appendicular joints evaluated were carpus, elbow, shoulder, tarsus, stifle and hip. Radiologic features evaluated and considered indicative of presence of DJD in appendicular joints were: joint effusion (not scored for the hip), osteophytes, enthesophytes, joint-associated mineralization, sclerosis, subluxation, subchondral bone erosions and cysts, presence of intraarticular mineralizations (including suspected meniscal mineralizations in the stifle joints) and new bone formation in the intertarsal and tarsometatarsal joints (tarsus only).

To ensure the evaluators carefully evaluated every feature, they were required to record a grade for each of the features listed above on a worksheet. Then they made and recorded a subjective overall assessment of DJD severity. A scale (0–4) was used for grading the severity of each of the radiographic changes identified (0 = normal; 1 = trivial; 2 = mild; 3 = moderate; 4 = severe). After this, a subjective radiographic DJD score (termed ''overall DJD score''; 0–10) where 0 = no radiographic abnormalities identified and 10 = ankylosis, was assigned to each joint based on presence of radiographic changes and their severity. This 2nd grading system was the one used for evaluation of prevalence of DJD (see Fig 1 for representative examples).

The axial skeleton was evaluated by dividing the spine into cervical, thoracic and lumbar segments, and lumbosacral region. Radiographic features evaluated and considered indicative of DJD in the axial skeleton were: osteophytes, spondylosis, disc-associated degeneration (end plate sclerosis, erosion, disc mineralization, narrowing), and subluxation. The same scale (0–4) and an overall subjective radiographic DJD score, as described for the appendicular joints, were assigned to each spinal segment based on presence of radiographic changes and their severity.

Figure 1 Representative radiographic images of elbows with various grades (0–10) of degenerative joint disease, illustrating the grading system used in the present study. Images opposite each other are orthogonal views of the same joint. A and B: grade 0; C and D: grade 1; E and F: grade 3; G–I: grade 6 (I is an oblique view showing suspected capsular mineralization); J and K: grade 9.

Data and Statistical Analysis

Agreement analysis was performed on the overall DJD scores for individual appendicular joints and spinal segments. This was done by calculating Fleiss' kappa (κ) statistic[10] for each of the overall DJD scores (0–10) and overall Fleiss' κ statistics and intraclass correlation (ICC) values for each of the joints. Additionally, the overall DJD scores assigned by each individual for each appendicular joint or spinal segment were redefined and grouped on a 1–5 scale as follows: 0 (1, none); 1 (2, trivial); 2–4 (3, mild); 5–7 (4, moderate); 8–10 (5, severe). This was done because not all the scores on the 0–10 scale had been used in assigning scores, making agreement analysis for individual scores impossible. Fleiss' κ statistics for each of the grouped DJD scores and overall κ statistics and ICC values for each of the appendicular joints and spinal segments were again calculated. Observer agreement κ and ICC values were interpreted as suggested by Landis and Koch[11]: ≤ 0 = no agreement; 0.0–0.2 = slight agreement; 0.2–0.4 = fair agreement; 0.4–0.6 = moderate agreement; 0.6–0.8 = substantial agreement; and 0.8–1.0 = almost perfect agreement.

To determine the overall DJD score for each appendicular joint or spinal segment of each cat, the median of the scores assigned by each of the 3 assessors was calculated.

Descriptive statistics were used to describe the number of cats with DJD in the appendicular and axial skeleton ("yes" or "no" approach); the summed severity for total, appendicular and axial DJD in each cat (where summed severity equaled the addition of all the individual overall DJD scores for every part of the skeleton, for all the appendicular joints or all the axial segments, respectively); the most frequently affected appendicular joints and spinal segments, and the median severity of DJD in each appendicular joint and spinal segment. The frequency of bilateral disease was also calculated.

Poisson's log-linear regression models were initially used to model appendicular, axial, and total DJD scores, each as a function of a single explanatory variable. The explanatory variables considered were sex, bodyweight, BCS, % of time spent indoors/outdoors, vaccination status (rabies, FeLV, FVRCP), use of flea/tick preventatives, FeLV and FIV status, hematologic, serum biochemical, and urinalysis profile variables. The Poisson regression model assumes that the response variable Y (in this case, appendicular, axial, or total DJD score) follows a Poisson distribution with $\log(E(Y|x)) = \alpha + \beta x$ where α and β are unknown parameters, x is an explanatory variable, and $E(Y|x)$ is the expected value

(mean) of Y given x. It follows that

$$\frac{E(Y|x+1)}{E(Y|x)} = \frac{\exp\{\alpha+\beta(x+1)\}}{\exp\{\alpha+\beta x\}} = \exp\{\beta\}$$

The result of this equation was used to describe how the explanatory variable x influences the expected value of Y: for each 1 unit increase in x, the expected value of Y changes by a multiplicative factor of exp {β}.

Sample variances of the DJD scores were greater than the sample means, so a quasi-Poisson regression model was used to account for over dispersion. The model was not adjusted by truncation to account for the natural maximum upper bound for the DJD scores because the estimated probability of observing a DJD score greater than the upper bound, obtained from fitting the quasi-Poisson regression model, was very small.

RESULTS

Twenty-five cats in each age group were successfully recruited and enrolled in the study. Of the owners contacted, 19 declined enrollment in the 6 month–5-year age group, 16 each in the 5–10 year and the 10–15 year groups, and 45 in the 15–20 year group. Of the 45 in the 15–20 year group, 16 were deceased. Of the 100 cats recruited, 18 were purebred and 82 were domestic short or long hair. Overall mean ($\pm$ SD) age was 9.42 ± 5.07 years. Mean bodyweight was 5.13 ± 1.64 kg (range, 2.08–10.16 kg). Median BCS was 3 (range, 1–5). Polyarthropathy was not suspected in any cat on physical examination. No morbidity or mortality occurred with the sedation protocol.

There was significant overall agreement (the null hypothesis of $\kappa = 0$ was rejected at the 99% confidence level for each body region) between observers when agreement was assessed using the individual overall DJD scores (1–10) assigned; however this agreement was only fair to moderate (Tables 1 and 2). When DJD scores were grouped into none, trivial, mild, moderate and severe (as described above), agreement between observers was improved, being fair for the pes, moderate for the carpus, elbow, shoulder and hip joints, and the cervical, thoracic, and lumbosacral spinal segments and substantial for the tarsal and stifle joints, and the lumbar spinal segment (Tables 3 and 4). The agreement between observers is summarized for each main appendicular joint and spinal segment using Tukey's mean-difference plots (Fig 2).

Ninety-one percent of the cats had at least 1 appendicular joint with DJD (median of 5 joints affected in the 91 cats; Fig 3). Figure 4 shows the observed total cat DJD score versus the cat age. The solid line shows the expected (or predicted) total DJD scores from the quasi-Poisson regression model. The most frequently affected joints were hip, followed by stifle, tarsus, and then elbow (Table 5). There was no difference between the number of joints affected on the right and left side. Fifty-five percent of the cats had axial skeleton DJD (median of 2 axial segments affected in the 55 cats). The thoracic segment was the most frequently affected, followed by the lumbosacral region (Table 6).

Overall, 92% of the cats had radiographic evidence of DJD somewhere in the skeleton. These cats had a mean age of 9.9 years and mean weight of 5.15 kg. The most severely affected joint was the elbow, and the most severely affected spinal segment was the lumbosacral region (Tables 5 and 6). Bilateral disease was common, particularly so for the hip, carpus, elbow, and stifle (Table 7).

There was no evidence of association between DJD scores and the variables sex, % of time spent indoors/outdoors, vaccination status (rabies, FeLV, FVRCP), use of flea/tick preventatives, and FeLV or FIV status. However, many of the explanatory variables considered were found to be significant predictors of appendicular DJD, axial DJD, and total DJD scores when considered individually (Tables 8–10).

Age was found to be the most important of the explanatory variables considered. When a more general quasi-Poisson regression model was used that included multiple explanatory variables simultaneously, no other explanatory variables were found to be significant after accounting for age. There was overwhelming evidence that the total DJD score changes with the age of a cat (P-value $< .0001$), and for each 1-year increase in the age of a cat, the expected total DJD score increases by an estimated 13.6% (95% confidence interval: 10.6–16.8% increase).

DISCUSSION

We found that the prevalence of DJD is high in domestic cats confirming previous retrospective studies[1–5,8]; however, the population we used for this prospective study may introduce some bias. Every attempt was made to randomly select subjects, and to that end, a single veterinary practice database was chosen. This was a feline-only veterinary practice and this may have introduced bias such as lifestyle, feeding, and veterinary care that may be different in these cats compared with the broader cat population as a

Table 1 Fleiss κ Values and 95% Confidence Intervals (CI) for Agreement Between Observers for Overall DJD Scores (0–10) for Different Musculoskeletal Regions

Manus	Estimate	CI Lower	CI Upper
Carpus	0.363	0.291	0.434
Elbow	0.335	0.279	0.391
Shoulder	0.443	0.369	0.518
Pes	0.327	0.213	0.440
Tarsus	0.524	0.465	0.584
Stifle	0.558	0.485	0.631
Hip	0.454	0.395	0.513
Cervical	0.358	0.293	0.423
Thoracic	0.534	0.469	0.599
Lumbar	0.448	0.380	0.516
Lumbosacral	0.512	0.452	0.573

All P-values $< .001$.
DJD, degenerative joint disease.

Table 2 ICC Values and 95% Confidence Intervals (CI) for Agreement Between Observers for Overall DJD Scores (0–10) for the Different Parts of the Musculoskeletal System Assessed

Manus	Estimate	CI Lower	CI Upper
Carpus	0.789	0.721	0.845
Elbow	0.850	0.799	0.891
Shoulder	0.917	0.887	0.941
Pes	0.330	0.206	0.457
Tarsus	0.896	0.859	0.925
Stifle	0.921	0.892	0.944
Hip	0.873	0.829	0.909
Cervical	0.753	0.677	0.818
Thoracic	0.794	0.728	0.849
Lumbar	0.800	0.735	0.854
Lumbo-sacral	0.868	0.822	0.905

All *P*-values $< .001$.
DJD, degenerative joint disease; ICC, intraclass correlation.

Table 4 ICC Values and 95% Confidence Intervals (CI) for Agreement between Observers for Grouped DJD Scores (1–5, Designating None, Trivial, Mild, Moderate, and Severe, Respectively)

Manus	Estimate	CI Lower	CI Upper
Carpus	0.668	0.575	0.750
Elbow	0.817	0.757	0.867
Shoulder	0.814	0.753	0.864
Pes	0.330	0.206	0.457
Tarsus	0.830	0.773	0.876
Stifle	0.852	0.801	0.893
Hip	0.788	0.720	0.844
Cervical	0.784	0.715	0.841
Thoracic	0.756	0.680	0.819
Lumbar	0.866	0.820	0.903
Lumbosacral	0.868	0.822	0.905

All *P*-values $< .001$.
DJD, degenerative joint disease; ICC, intraclass correlation.

whole. Cats in our study were from the central North Carolina region of the United States of America, and geographical differences in the prevalence of DJD may exist between populations because of environmental or genetic influences, just as they do in people.[12]

We spent considerable time very precisely defining what features were to be classified as indicative of DJD in cats. There is very little information on the association between radiographic features and gross or histologic features of DJD in feline joints, and it is possible the features we assessed were not indicative of actual joint pathology. We found that several radiographic features not normally observed in canine patients (such as medial meniscal mineralization and periarticular mineralizations were seen commonly in these cats. It could be argued that the inclusion of such features as indicative of DJD is erroneous, but we included such features on the basis of other work we have performed that has demonstrated an association between those features and DJD as measured by macroscopic cartilage damage. For example, we have observed that joints with only meniscal mineralization, and no other features of DJD, predictably have cartilage erosion.[13] In the present study, joints with only meniscal mineralization were therefore included in the "DJD" category. Previous studies have included such features as periarticular mineralization as being indicative of DJD.[5] Despite long discussions spent defining what each assessor was going to score as DJD, agreement between the observers was only fair to moderate, and improved when several broad categories of severity of DJD were used. The more score options there are for the radiologist to choose from the more likely their scores would not match exactly. For this reason, and because it is maybe more appropriate in the clinical environment, we combined scores into groups. It was clear from conducting this study and a previous pilot study, that further work is needed to define the features of feline DJD.

Table 3 Fleiss κ Values and 95% Confidence Intervals (CI) for Agreement Between Observers for Grouped DJD Scores (1–5, Designating None, Trivial, Mild, Moderate, and Severe, Respectively)

Manus	Estimate	CI Lower	CI Upper
Carpus	0.401	0.317	0.486
Elbow	0.536	0.463	0.610
Shoulder	0.488	0.409	0.567
Pes	0.327	0.213	0.440
Tarsus	0.602	0.527	0.676
Stifle	0.614	0.538	0.691
Hip	0.565	0.493	0.636
Cervical	0.571	0.495	0.646
Thoracic	0.523	0.442	0.605
Lumbar	0.624	0.552	0.696
Lumbosacral	0.512	0.452	0.573

All *P*-values $< .001$.
DJD, degenerative joint disease.

To our knowledge, this is the first prospective study to evaluate every part of the skeletal system for DJD in a randomly selected cohort of cats. Similar to previous retrospective reports of axial skeleton DJD[3–5] the most commonly affected spinal region was the thoracic segment, followed by the lumbosacral area. However, the thoracic segment has more vertebrae than other areas, which may introduce a bias for it to be affected more often. Others have suggested the lumbosacral area is the most severely affected spinal segment in the cat.[4] Review of published retrospective studies suggests they support the current finding of a strong association between the prevalence of axial DJD and age.[3–5] Although it appears that investigators are describing the same general findings for axial skeleton DJD, the nomenclature used varies, as do the features included as being indicative of axial DJD.[2–5,14] This problem has been recently discussed.[15] Further studies are needed to accurately define the features of axial skeleton DJD.

The very high prevalence of appendicular skeleton DJD, and its association with age in our study is supported by previous reports.[4,5,8,16] We found the most commonly affected appendicular joints were the hip, followed by stifle, tarsus, and elbow. Previous reports have suggested the elbow[1,4,8,16] and hip[2,5] as being most commonly affected. Only 2 of these studies[1,2] involving a total of 41 cats

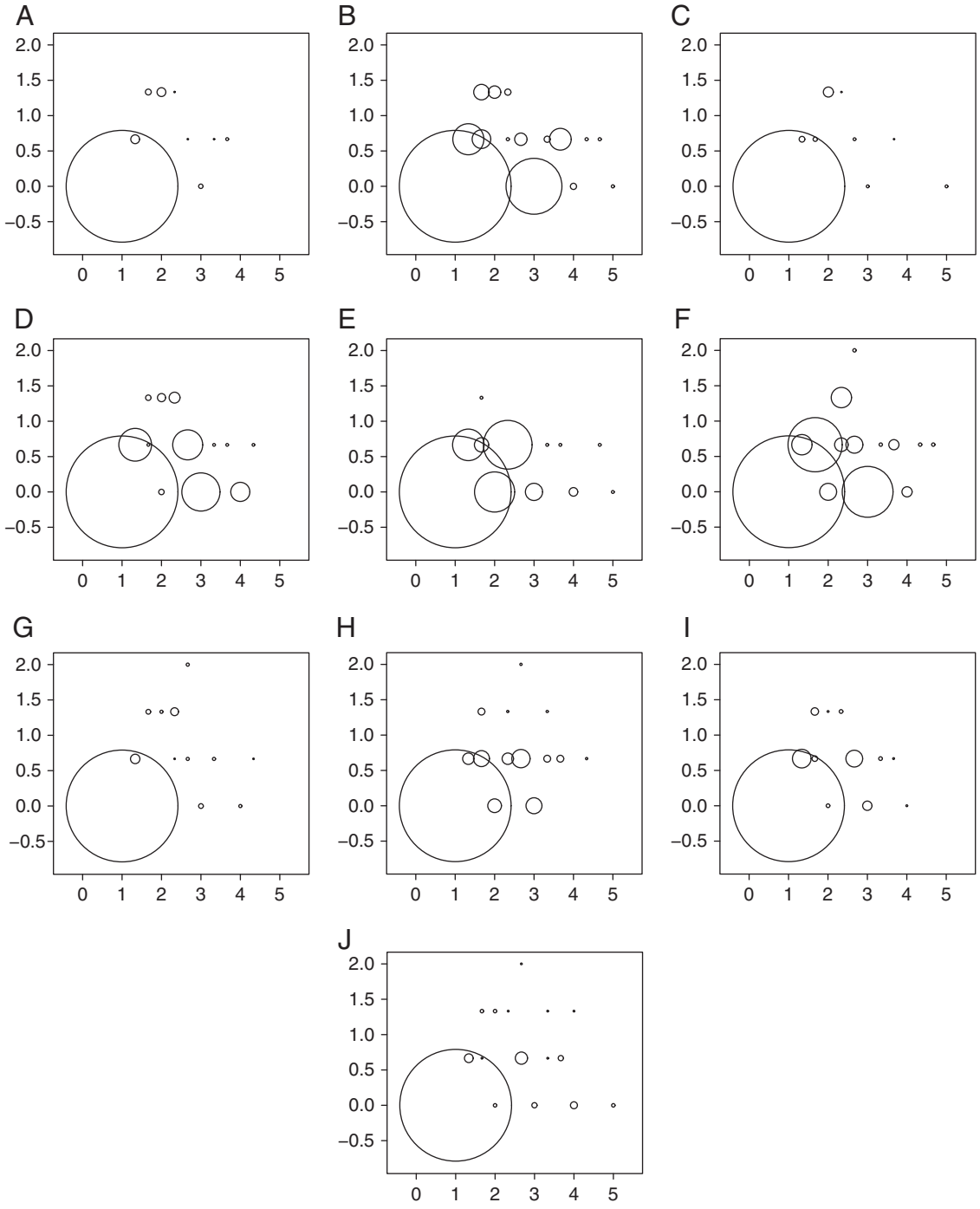

Figure 2 Tukey's mean difference plots to summarize the interobserver agreement (A = carpus; B = elbow; C = shoulder; D = tarsus; E = stifle; F = hip; G = cervical spine; H = thoracic spine; I = lumbar spine; J = lumbosacral spine). On the x-axis are the average scores using the 1–5 scale created by collapsing the 1–10 overall degenerative joint disease (DJD) scores (1, none = overall DJD scores of 0; 2, trivial = overall DJD scores of 1; 3, mild = overall DJD scores of 2–4); 4, moderate = overall DJD scores of 5–7; 5, severe = overall DJD scores of 8–10), and on the y-axis is the average of the absolute value of the differences of the scores between observers. The area of the circle is proportional to the number of times that the (x,y) points occurred for the 100 cats.

evaluated every joint. The other studies evaluated radiographs that were available (often thorax or abdomen), and so bias was introduced because only certain joints were visible on the radiographs. We included meniscal mineralization as indicative of DJD, and this contributed to the high prevalence of DJD in the stifle joint. This was done because

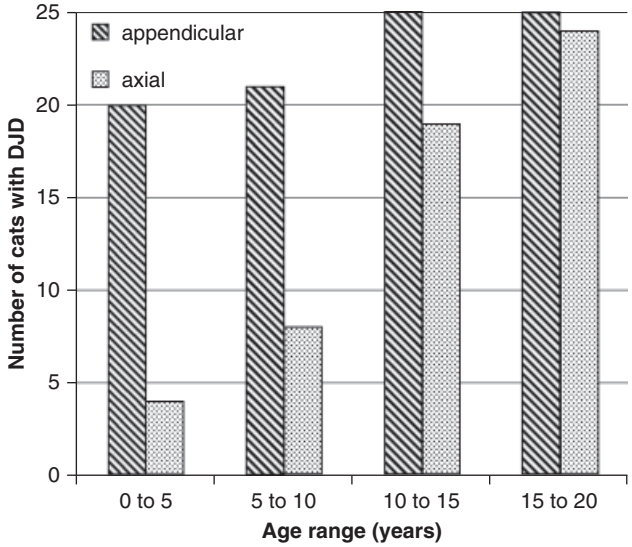

Figure 3 Prevalence of appendicular and of axial radiographic degenerative joint disease (DJD) in cats in different age ranges (n = 25 cats in each age range). Cats that were exactly 5, 10, or 15 years old were assigned to the 6 months–5 years, 5–10 years, and 10–15 years groups, respectively.

of our gross and histologic observations that meniscal mineralization, despite some suggestions in the literature,[17–20] is associated with cartilage degeneration.[13]

We found a high percentage of joints to be bilaterally affected with DJD. In a study of 292 sets of feline radiographs (mean cat age not reported but mean age of clinic population, 8.2 years) evaluated for appendicular OA (defined as increased subchondral bone density or periarticular new bone),[8] lesions were bilaterally symmetrical in 41 (73%) of the 56 affected cats, with the elbow most commonly affected.

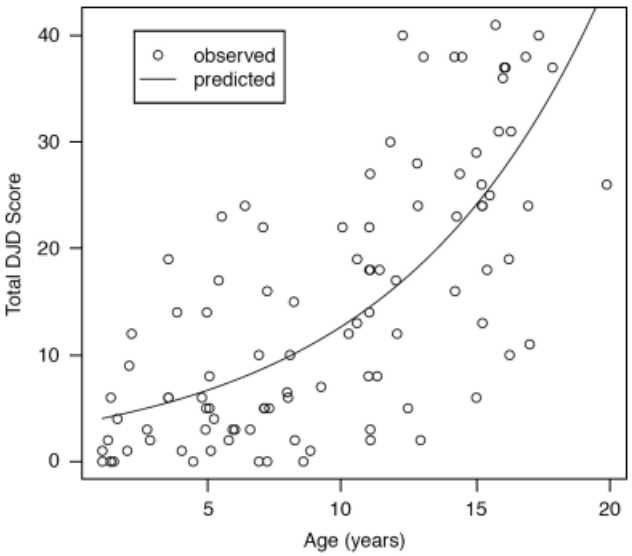

Figure 4 Observed total cat degenerative joint disease (DJD) score (sum of individual appendicular joint and axial skeleton segment overall DJD scores) versus the age of the cat. The solid line shows the expected (or predicted) total DJD scores from the quasi-Poisson regression model.

Table 5 Number of Individual Joints Affected with DJD in 100 Randomly Selected Cats, and Median Overall DJD Score (on a 0–10 Scale) per Joint

Joint	Number (%) of Joints Affected	Median (Range) DJD Score
Hip	131 (65%)	2 (1–8)
Stifle	102 (50%)	1 (1–9)
Tarsus	85 (40%)	2 (1–7)
Elbow	69 (35%)	3 (1–9)
Carpus	32 (15%)	2 (1–7)
Shoulder	28 (14%)	2 (1–8)
Pes	1 (0.5%)	–
Manus	0 (0%)	–

The manus and pes were considered 1 joint.
DJD, degenerative joint disease.

Table 6 Number of Individual Spinal Segments Affected with DJD in 100 Randomly Selected Cats, and Median Overall DJD Score (on a 0–10 Scale) per Spinal Segment

Spinal Segment	Number of Cats Affected	Median (Range) DJD Score
Thoracic	43	2 (1–7)
Lumbosacral	29	4 (1–10)
Lumbar	26	2.5 (1–6)
Cervical	20	3 (1–7)

DJD, degenerative joint disease.

Overall, despite the high prevalence of radiographic DJD, the severity scores were relatively low. This may reflect the particular population studied or that the radiographic severity of DJD in cats may be less than in dogs. This suggestion has been made in previous studies and needs further investigation.[4,5]

As individual variables, bodyweight and BCS were found to be negatively associated with the severity of axial DJD, but no association was found between these variables and appendicular or total DJD. Anecdotally, it is often suggested that obesity causes DJD in cats, which would suggest a positive relationship would be identified. A causal relationship has not been proven, but the relationship between being overweight and lameness requiring veterinary care has been evaluated. Studying 1457 cats over a 4.5-year

Table 7 Prevalence of Bilateral DJD in Appendicular Joints

Joint	Number of Cats with DJD of One or Both Joints	Number of Cats with DJD of Both Left and Right Joints	% of Cats with DJD that have DJD of Both Left and Right Joints
Manus	0	0	0
Carpus	19	13	68
Elbow	41	28	68
Shoulder	20	8	40
Pes	1	0	0
Hock	55	30	55
Stifle	63	39	62
Hip	73	58	79

DJD, degenerative joint disease.

Table 8 Summary Results from Fitting Quasi-Poisson Regression Models Using Each Individual Explanatory Variable and its Relationship to the Presence of Appendicular DJD

Explanatory Variable	*P*-Value for Association with DJD	Level of Evidence of Significance	Relationship Between Variable and DJD (Positive, +; Negative, −)	Estimated % of the Expected DJD Score Increases or Decreases for Each 1 Unit Increase in the Explanatory Variable
Age (years)	.0000	Overwhelming	+	10.31
Lipase (IU/L)	.0000		+	1.75
Urine pH	.0010	Very strong	−	30.43
Urine specific gravity	.0011		−	0.06
Lymphocytes (10^3/μL)	.0012		−	0.02
% Dry food consumed	.0014		−	0.70
Creatinine (mg/dL)	.0015		+	51.39
Urea nitrogen (mg/dL)	.0023		+	2.30
Cholesterol (mg/dL)	.0044		+	0.51
Amylase (IU/L)	.0072		+	0.07
Sodium (mmol/L)	.0180	Strong	+	7.57
Glucose (mg/dL)	.0183		−	0.31
Fructosamine (mmol/L)	.0198		−	0.38
Magnesium (mg/dL)	.0369		+	76.71
Hemolysis index	.0506	Suggestive but inconclusive	−	0.94
CK (IU/L)	.0598		−	0.03
Osmolality—calculated (mOsm/kg)	.0671		+	2.42
Chloride (mmol/L)	.0810		+	2.14

DJD, degenerative joint disease.

period, investigators found that the risk of developing lameness requiring veterinary attention was significantly increased for heavy (hazard ratio = 2.9) and obese (hazard ratio = 4.9) cats.[21] It was suggested that excess bodyweight or a generalized lipid metabolic abnormality might lead to cartilage damage and OA; however, the cause of lameness and specifically if it was associated with DJD was not evaluated. In 1 retrospective radiographic study of the

Table 9 Summary Results from Fitting Quasi-Poisson Regression Models Using Each Individual Explanatory Variable and its Relationship to the Presence of Spinal DJD

Explanatory Variable	*P*-Value for Association with DJD	Level of Evidence of Significance	Relationship Between Variable and DJD	Estimated % of the Expected DJD Score Increases or Decreases for Each 1 Unit Increase in the Explanatory Variable
Age (years)	.0000	Overwhelming	+	27.77
Sodium (mmol/L)	.0000		+	22.86
Urine pH	.0000		−	59.13
Urea nitrogen (mg/dL)	.0001		+	4.87
Urine specific gravity	.0002		−	0.11
Glucose (mg/dL)	.0003		−	0.86
Creatinin (mg/dL)	.0004		+	109.95
Osmolality—calculated (mOsm/kg)	.0011	Very strong	+	7.03
Lipase (IU/L)	.0022		+	2.15
% Dry food consumed	.0030		−	1.11
BCS	.0032		−	32.63
Weight (kg)	.0033		−	27.68
Amylase (IU/L)	.0046		+	0.11
Chloride (mmol/L)	.0075		+	4.33
Bilirubin total (mg/dL)	.0088		−	99.99
Fructosamine (mmol/L)	.0159	Strong	−	0.61
Phosphorus (mg/dL)	.0220		+	49.33
Lymphocytes (10^3/μL)	.0315		−	0.03
Monocytes (10^3/μL)	.0465		+	0.11
CK (IU/L)	.0502	Suggestive but inconclusive	−	0.06
Hemolysis index	.0542		−	2.37
Calcium (mg/dL)	.0542		+	39.25
Alkaline phosphatase (IU/L)	.0551		+	1.54
Na/K ratio	.0784		+	6.14

BCS, body condition score.

Table 10 Summary Results from Fitting Quasi-Poisson Regression Models Showing Significant Individual Explanatory Variables and their Relationship to the Presence of Total DJD

Explanatory Variable	*P*-Value for Association with DJD	Level of Evidence of Significance	Relationship Between Variable and DJD	Estimated % of the Expected DJD Score Increases or Decreases for Each 1 Unit Increase in the Explanatory Variable
Age (years)	.0000	Overwhelming	+	13.61
Lipase (IU/L)	.0000		+	1.86
Urine pH	.0000		–	37.95
Urine specific gravity	.0001		–	0.07
Urea nitrogen (mg/dL)	.0001		+	2.98
Creatinine (mg/dL)	.0001		+	65.27
% Dry food consumed	.0003		–	0.81
Sodium (mmol/L)	.0005		+	11.31
Lymphocytes ($10^3/\mu L$)	.0011	Very strong	–	0.02
Glucose (mg/dL)	.0011		–	0.45
Amylase (IU/L)	.0013		+	0.08
Osmolality—calculated (mOsm/kg)	.0065		+	3.62
Fructosamine (mmol/L)	.0070		–	0.45
Cholesterol (mg/dL)	.0130	Strong	+	0.47
Chloride (mmol/L)	.0165		+	2.79
CK (IU/L)	.0257		–	0.04
Hemolysis index	.0260		–	1.19
Calcium (mg/dL)	.0512	Suggestive but inconclusive	+	22.72
Bilirubin total (mg/dL)	.0513		–	98.93
Monocytes ($10^3/\mu L$)	.0745		+	0.07
BCS	.0752		–	12.53

BCS, body condition score; DJD, degenerative joint disease.

prevalence of DJD in cats, no significant association between bodyweight and radiographic signs of DJD was identified.[5] The initial finding of a negative association between bodyweight and axial DJD is likely explained by the effect of age on bodyweight—with older cats becoming lighter. It is known that cats tend to loose weight and BCS as they age.[22,23]

We did not specifically categorize the DJD as primary or secondary, but subjectively, there were very few joints where any radiographic indications of a cause were seen (e.g. trauma), and in no case was a polyarthropathy suspected. The cause of most feline DJD is unknown, and we thought that evaluation of several variables (patient demographics and serum biochemical, hematologic and urine analysis profile variables) may lead to testable hypotheses for the cause(s) of feline DJD. Overall, once age was accounted for, there were no variables that were significantly associated with DJD, and further interpretation of the results of our study should be performed cautiously. However, this simplistic view ignores the possibility that there may be associations between some variables and DJD. For example, chronic kidney disease is known to become more prevalent in older cats, but it may be that the same pathologic processes causing chronic kidney disease also cause DJD. Lipase was very strongly associated with DJD, possibly indicating an association between an inflammatory process (that is also associated with age) and DJD, or the association may be the result of decreased renal function leading to decreased excretion of lipase. This is speculation and further studies are required to test specific hypotheses.

The apparent negative association between appendicular DJD and feeding a dry diet is probably because of the strong association between age and type of diet fed—the older the cat in our cohort, the more likely they were to be fed a higher % of their diet as wet food. This likely reflects the recommendations of the practice this cohort of cats was recruited from strongly recommending feeding wet food to older cats.

We found a very high prevalence of appendicular and axial skeleton DJD in domesticated cats. DJD may indeed be the most common disease of domesticated cats, and the significance of these findings in terms of joint pathology and clinical signs requires investigation.

ACKNOWLEDGMENTS

This study was funded by Novartis Animal Health, through their competitive grants program. The authors have no financial or personal relationships that could possibly influence or inappropriately bias this work.

REFERENCES

1. Clarke SP, Bennett D: Feline osteoarthritis: a prospective study of 28 cases. *J Small Anim Pract* 2006;47:439–445
2. Lascelles BD, Hansen BD, Roe S, et al: Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *J Vet Intern Med* 2007;21:410–416

3. Beadman R, Smith RN, King AS: Vertebral osteophytes in the cat. *Vet Rec* 1964;76:1005–1007
4. Hardie EM, Roe SC, Martin FR: Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). *J Am Vet Med Assoc* 2002;220:628–632
5. Clarke SP, Mellor D, Clements DN, et al: Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. *Vet Rec* 2005;157:793–799
6. Langenbach A, Green P, Giger U, et al: Relationship between degenerative joint disease and hip joint laxity by use of distraction index and Norberg angle measurement in a group of cats. *J Am Vet Med Assoc* 1998;213:1439–1443
7. Keller GG, Reed AL, Lattimer JC, et al: Hip dysplasia: a feline population study. *Vet Radiol Ultrasound* 1999;40: 460–464
8. Godfrey DR: Osteoarthritis in cats: a retrospective radiological study. *J Small Anim Pract* 2005;46:425–429
9. German A, Martin L: *Feline Obesity, in Encyclopedia of Feline Clinical Nutrition*. Aimargues, Royal Canin, 2008, pp 16
10. Fleiss JL: *Statistical Methods for Rates and Proportions* (ed 2). New York, John Wiley, 1981
11. Landis JR, Koch GG: The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174
12. Ali-Gombe A, Croft PR, Silman AJ: Osteoarthritis of the hip and acetabular dysplasia in Nigerian men. *J Rheumatol* 1996;23:512–515
13. Freire M, Brown J, Robertson I, et al: Meniscal mineralization in domestic cats. *Vet Surg* 2010, doi: 10.1111/ j.1532-950X.2010.00648.x.
14. Rothschild BM, Rothschild C, Woods RJ: Inflammatory arthritis in large cats: an expanded spectrum of spondyloarthropathy. *J Zoo Wildl Med* 1998;29:279–284
15. Lascelles BD: Feline degenerative joint disease. *Vet Surg* 2010;39:2–13
16. Pacchiana PD, Gilley RS, Wallace LJ, et al: Absolute and relative cell counts for synovial fluid from clinically normal shoulder and stifle joints in cats. *J Am Vet Med Assoc* 2004; 225:1866–1870
17. Ganey TM, Ogden JA, Abou-Madi N, et al: Meniscal ossification. II. The normal pattern in the tiger knee. *Skeletal Radiol* 1994;23:173–179
18. Reinke J, Mughannam A: Meniscal calcification and ossification in six cats and two dogs. *J Am Anim Hosp Assoc* 1994;30:145–152
19. Walker M, Phalan D, Jensen J, et al: Meniscal ossicles in large non-domestic cats. *Vet Radiol Ultrasound* 2002;43: 249–254
20. Whiting PG, Pool RR: Intrameniscal calcification and ossification in the stifle joints of three domestic cats. *J Am Anim Hosp Assoc* 1984;21:579–584
21. Scarlett JM, Donoghue S: Associations between body condition and disease in cats. *J Am Vet Med Assoc* 1998;212:1725–1731
22. Kronfeld DS, Donoghue S, Glickman LT: Body condition of cats. *J Nutr* 1994;124:2683S–2684S
23. Laflamme DP: Nutrition for aging cats and dogs and the importance of body condition. *Vet Clin North Am Small Anim Pract* 2005;35:713–742

PUBLICATION 2

Radiographic evaluation of feline appendicular degenerative joint disease versus macroscopic appearance of articular cartilage. Freire M, Robertson I, Bondell HD, Brown J, Hash J, Pease AP, Lascelles BD. *Veterinary Radiology & Ultrasound*. 2011;52(3):239-47.

http://www.ncbi.nlm.nih.gov/pubmed/21418370

RADIOGRAPHIC EVALUATION OF FELINE APPENDICULAR DEGENERATIVE JOINT DISEASE VS. MACROSCOPIC APPEARANCE OF ARTICULAR CARTILAGE

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Degenerative joint disease (DJD) is common in domesticated cats. Our purpose was to describe how radiographic findings thought to indicate feline DJD relate to macroscopic cartilage degeneration in appendicular joints. Thirty adult cats euthanized for reasons unrelated to this study were evaluated. Orthogonal digital radiographs of the elbow, tarsus, stifle, and coxofemoral joints were evaluated for the presence of DJD. The same joints were dissected for visual inspection of changes indicative of DJD and macroscopic cartilage damage was graded using a Total Cartilage Damage Score. When considering all joints, there was statistically significant fair correlation between cartilage damage and the presence of osteophytes and joint-associated mineralizations, and the subjective radiographic DJD score. Most correlations were statistically significant when looking at the different joints individually, but only the correlation between the presence of osteophytes and the subjective radiographic DJD score with the presence of cartilage damage in the elbow and coxofemoral joints had a value above 0.4 (moderate correlation). The joints most likely to have cartilage damage without radiographic evidence of DJD are the stifle (71% of radiographically normal joints) followed by the coxofemoral joint (57%), elbow (57%), and tarsal joint (46%). Our data support radiographic findings not relating well to cartilage degeneration, and that other modalities should be evaluated to aid in making a diagnosis of feline DJD. © 2011 *Veterinary Radiology & Ultrasound, Vol. 52, No. 3, 2011, pp 239–247.*

Key words: cartilage damage, cat, DJD, macroscopic, radiographs.

Introduction

FELINE DEGENERATIVE JOINT disease (DJD) is common in domesticated cats.[1–5] The high prevalence has generated interest in describing the clinical signs, evaluating causes and predisposing factors, and measuring the pain associated with the radiographic changes.[6–12] Despite this interest, there is no information on how the radiographic findings of feline DJD relate to actual degeneration of the various joint components, such as cartilage.

Grading of DJD in animals and human patients is usually performed using radiographic imaging and evaluation of cartilage changes during surgery or arthroscopy. However, the usefulness of various radiographic features of DJD for prediction of articular cartilage degeneration is not well documented in any species. In humans, marginal osteophytes may be the most sensitive radiographic feature for the detection of articular cartilage degeneration in the patellofemoral joint.[13,14]

Historically, radiographic criteria used to assess canine DJD have been applied to cats [2–4] and it has been assumed that these criteria are indicative of joint tissue degeneration. However, some have suggested that the radiographic features of DJD in the cat are different to those in the dog.[5] Others have suggested that cats do not form osteophytes as readily as dogs[2,3,5,10]; while still others have suggested radiographically normal joints can be a source of pain due to DJD.[3,8] Clearly, there is a need to understand how the radiographic features of feline DJD relate to joint tissue degeneration.

High-resolution analog radiographs have increased spatial resolution compared with digital radiographs. Although digital radiographs have poorer spatial resolution, considered important in feline orthopedic imaging, the associated enhanced dynamic range and postprocessing capabilities can lead to an overall improvement in diagnostic performance.[15] There are no studies comparing analog vs. digital imaging systems with respect to feline extremities.

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Funding was provided by Novartis Animal Health, through their global Fellowship Research program.

This study was completed at the North Carolina State University College of Veterinary Medicine, Raleigh, NC.

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Received June 27, 2010; accepted for publication January 18, 2011.
doi: 10.1111/j.1740-8261.2011.01803.x

We hypothesize (null hypotheses) there is no difference between the sensitivity of digital and analog radiographs for the detection of radiographic signs of DJD in feline joints and secondly, that there is no association between radiographic features of DJD and the presence of macroscopically detectable articular cartilage damage in feline appendicular joints.

Materials and Methods

Thirty adult cats euthanized at a local animal shelter with an overdose of barbiturates for population control were studied. We aimed to identify 15 cats with multiple joint DJD and 15 without radiographically detectable DJD. We also aimed to have both radiographically normal joints and joints with varying degrees of radiographic DJD. The breeds were domestic short hair (23), domestic long hair (2), domestic medium hair (2), Main Coon (1), Abyssinian (1), and Himalayan (1). They were nine neutered male, two intact male, six neutered female, and 13 female cats; cats were considered neutered female when neuter status was not known. The mean (± SD) age of the cats was 12 years (± 4); age was known in 25 cats. Mean weight was 4.75 kg (± 0.957) and the median body condition score was 3/5. A total of 60 elbow, 60 tarsal, 60 stifle, and 59 coxofemoral joints were included in the study. One coxofemoral joint was excluded because of the presence of an intraarticular fracture of the femoral head.

Within 1 h of euthanasia, orthogonal radiographs of the elbow (medio-lateral and caudo-cranial views), tarsus (medio-lateral and dorso-plantar views), stifle (medio-lateral and cranio-caudal views), and coxofemoral joints (lateral and extended ventro-dorsal views) were made using an indirect digital flat panel imaging system* and high detail film/screen (analog) system.†,‡

The digital and analog radiographs were evaluated by a group of three board-certified veterinary radiologists (I.R., J.B., A.P.) and one board-certified veterinary surgeon (B.D.X.L.). Assessments were the consensus of all individuals. Digital radiographs were viewed using Dell Ultrasharp 2407WFP color monitors (24″ LCD resolution of 1920 × 1200) and standard medical image viewing software.§ Evaluations were performed without knowledge of the age, breed, gender, or macroscopic appearance of the joints. Using radiographs from 10 randomly selected cats, the assessors discussed what radiographic features to score that were indicative of DJD. Radiographic features decided upon were increased soft tissue opacity within the joint considered compatible with joint effusion, osteophytes, enthesophytes, joint-associated mineralization—extraarticular mineralizations considered to be outside the joint, possibly associated with joint capsule or tendons, sclerosis, subchondral bone erosions/cysts, coxofemoral subluxation, intraarticular mineralizations—including meniscal mineralizations, and new bone formation on the dorsal surface of intertarsal and tarsometatarsal joints.

A severity scale from 0 to 4, constructed by the assessors, was used for grading the severity of each radiographic change (0 normal, 1 trivial, 2 mild, 3 moderate, 4 severe) for each joint. Following this a subjective radiographic DJD score (DJD/10) from 0 to 10 (0—no radiographic abnormalities identified; 10—ankylosis) was assigned to each joint based on the presence of radiographic changes and their severity.

Following radiographic evaluation, each joint was opened carefully by one of the authors (M.F.), who did not participate in radiographic interpretation, for visual inspection and evaluation of degenerative changes. Macroscopic changes considered indicative of DJD were osteophytes, joint-associated mineralization, and cartilage damage.

Osteophytes were graded according to the osteophyte scoring system described in a previous study[16]: Grade 0—normal; Grade 1—small osteophytes; Grade 2—medium osteophytes; Grade 3—large osteophytes. Joint-associated mineralizations were graded based on size using the following scale: Grade 0—none; Grade 1—mild mineralization; Grade 2—moderate mineralization; Grade 3—large/extensive mineralization. The surface appearance of the joints was evaluated grossly for fibrillation and/or erosion of the articular cartilage using application of India ink as described previously.[17] The cartilage surface was painted with India ink twice, rinsing the cartilage with water each time, 3 min after the ink was applied. The severity of surface cartilage damage was scored based on ink retention, and graded according to the scale described in a previous study[18]:Grade 1—Intact surface: surface appears normal and does not retain any ink; Grade 2—Minimal fibrillation: site appears normal before staining, but retains India ink as elongated specks or light grey patches; Grade 3—Overt fibrillation: the cartilage is velvety in appearance and retains ink as intense black patches. Grade 4—Erosion: loss of cartilage exposing the underlying bone.

The severity of articular cartilage damage for each joint was quantified as the Total Cartilage Damage Score, which was the sum of the Cartilage Damage Score of each main articular surface of that joint. The Cartilage Damage Score of each of those areas was calculated as the percent of the total articular cartilage area damaged, multiplied by the degree of cartilage damage for that area based on the ink retention grading system. The Cartilage Damage Score ranged from 0 to 400 (0—no cartilage damage; 400—complete exposure of subchondral bone over the whole of the

*Canon Medical CXDI-50G Sensor, Eklin Medical Systems, Santa Clara, CA.
†Kodak Lanex Fine screens, Carestream Health, Rochester, NY.
‡Super HR-U 30 X-ray film, Fuji Medical Systems, Stamford, CT.
§eFilm 2.1.2Merge Healthcare, Milwaukee, WI.

articular surface) and was calculated using the following equation:

$$\begin{aligned}&\text{Cartilage Damage Score}\\&= [\%\text{area}_1 \times \text{ink grade}_{\text{area 1}}]\\&\quad + [\%\text{area}_2 \times \text{ink grade}_{\text{area 2}}] + \cdots\end{aligned}$$

The Total Cartilage Damage Score was the addition of the Cartilage Damage Score for each main articular surface(s) of each bone comprising the joint:

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{elbow}}\\&= \text{Cartilage Damage Score}_{\text{ulna}}\\&\quad + \text{Cartilage Damage Score}_{\text{radius}}\\&\quad + \text{Cartilage Damage Score}_{\text{humerus}}\end{aligned}$$

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{coxofemoral}}\\&= \text{Cartilage Damage Score}_{\text{acetabulum}}\\&\quad + \text{Cartilage Damage Score}_{\text{femoral head}}\end{aligned}$$

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{tarsus}}\\&= \text{Cartilage Damage Score}_{\text{talus}}\\&\quad + \text{Cartilage Damage Score}_{\text{tibia}}\end{aligned}$$

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{stifle}}\\&= \text{Cartilage Damage Score}_{\text{femur med condyle}}\\&\quad + \text{Cartilage Damage Score}_{\text{femur lat condyle}}\\&\quad + \text{Cartilage Damage Score}_{\text{femur trochlea}}\\&\quad + \text{Cartilage Damage Score}_{\text{tibia med condyle}}\\&\quad + \text{Cartilage Damage Score}_{\text{tibia lat condyle}}\\&\quad + \text{Cartilage Damage Score}_{\text{patella}}\end{aligned}$$

Total Cartilage Damage Score values ranged from 0 to 1200 in the elbow, 2400 in the stifle, 800 in the tarsus, and 800 in the coxofemoral joint (0—no cartilage damage present; highest value—complete exposure of subchondral bone in all articular surfaces evaluated).

To calculate the Cartilage Damage Score and Total Cartilage Damage Score, digital photographs of the major joint surfaces, after the second application and washing off of India ink, were made in exactly the same way in each joint. Computer software¶ was used to calculate the percent of the cartilage area retaining India ink as a result of cartilage fibrillation.

To assess the correlation between the analog and digital radiographic scores Kendall's τ correlation coefficient was used. The radiographic scores considered were: subjective overall radiographic DJD score for the joint (0–10), Yes/No DJD (whether or not DJD was present; score 1–0) and the main radiographic features considered indicative of DJD (scored on the 0–4 scale).

After the digital and analog radiographic scores were correlated, Wilcoxon's signed-rank test was used to compare the sensitivity of the two systems. As a result of these comparisons, digital radiographic data were used in the remainder of the study.

The prevalence of radiographic signs of DJD in digital radiographs and macroscopic evidence of cartilage damage was characterized using descriptive statistics. The correlation between the India ink score for each joint and the subjective radiographic DJD score (DJD/10) as well as the severity scores for the main radiographic features of DJD was computed using Kendall's τ correlation coefficient. Kendall's τ coefficient results were interpreted as follows: 0, negative correlation; 0–0.2, slight correlation; 0.21–0.4, fair correlation; 0.41–0.6, moderate correlation; 0.61–0.8, substantial correlation; 0.81–1, almost perfect correlation.

The mean ($\pm$ SD) Total Cartilage Damage Score for those joints with an overall subjective radiographic DJD score of 0 was calculated to quantify the degree of cartilage damage present when there were no radiographic signs of DJD. Finally, multiple linear regression was used in each joint to investigate for relationships between the magnitude of Total Cartilage Damage Score and age, weight, gender, BCS, and each of the radiographic findings considered indicative of DJD. The models used were expressed by

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{elbow}}\\&= \beta_0 + \beta_1 \times \text{DJD}/10\\&\quad + \beta_2 \times \text{osteophytes}\\&\quad + \beta_3 \times \text{joint-associated mineralizations}\\&\quad + \beta_4 \times \text{sclerosis}\\&\quad + \beta_5 \times \text{effusion}\\&\quad + \beta_6 \times \text{enthesophytes}\\&\quad + \beta_7 \times \text{erosions/cysts}\\&\quad + \beta_8 \times \text{age}\\&\quad + \text{error}\end{aligned}$$

$$\begin{aligned}&\text{Total Cartilage Damage Score}_{\text{tarsus}}\\&= \beta_0 + \beta_1 \times \text{DJD}/10\\&\quad + \beta_2 \times \text{osteophytes}\\&\quad + \beta_3 \times \text{joint-associated mineralizations}\\&\quad + \beta_4 \times \text{sclerosis}\\&\quad + \beta_5 \times \text{effusion}\\&\quad + \beta_6 \times \text{enthesophytes}\\&\quad + \beta_7 \times \text{fusion mineralization}\\&\quad + \beta_8 \times \text{erosions/cysts}\\&\quad + \beta_9 \times \text{age}\\&\quad + \text{error}\end{aligned}$$

¶Adobe Photoshop 7.0, Adobe, CA.

$$\text{Total Cartilage Damage Score}_{\text{stifle}} = \beta_0 + \beta_1 \times \text{DJD}/10 + \beta_2 \times \text{osteophytes} + \beta_3 \times \text{joint-associated mineralizations} + \beta_4 \times \text{sclerosis} + \beta_5 \times \text{effusion} + \beta_6 \times \text{enthesophytes} + \beta_7 \times \text{intraarticular mineralizations} + \beta_8 \times \text{meniscal mineralization} + \beta_9 \times \text{erosions/cysts} + \beta_{10} \times \text{age} + \text{error}$$

$$\text{Total Cartilage Damage Score}_{\text{coxofemoral}} = \beta_0 + \beta_1 \times \text{DJD}/10 + \beta_2 \times \text{osteophytes} + \beta_3 \times \text{joint-associated mineralizations} + \beta_4 \times \text{sclerosis} + \beta_5 \times \text{subluxation} + \beta_6 \times \text{erosions/cysts} + \beta_7 \times \text{age} + \text{error}$$

Total Cartilage Damage Score = Dependent variable

$\beta_0, \beta_1, \ldots \beta_n$ = contribution of each independent variable to the prediction of the dependent variable.

In all analyses, $P<0.05$ was considered significant.

RESULTS

Significant correlation was found between digital and analog radiographic scores for all features except joint-associated mineralizations in the stifle and enthesophytes in the tarsal joint (Table 1). Either there were no differences between analog vs. digital radiographic scores or digital radiographic scores were higher than analog radiographic scores (Table 2). Hence, digital radiographs were considered more sensitive in the detection of the radiographic features studied.

Of the 239 joints evaluated for radiographic changes indicative of DJD, changes were found in 127 joints (53%).

Evaluation of Digital Radiographs

Elbow Joint

Twenty-five (42%) of the 60 elbows had radiographic signs of DJD with a median subjective radiographic DJD score of 3 (range, 1–5). Joint-associated mineralizations were identified in 18 elbow joints (72% of joints with radiographic signs of DJD), osteophytes in 16 joints (64%), enthesophytes in four joints (16%), and sclerosis of the

TABLE 1. Correlation between Digital and Analog Radiographs Assessing Subjective Radiographic DJD/10 score, Yes/No DJD Score and Main Radiographic Features Considered Indicative of DJD in Each Joint, Expressed by Kendall's τ Correlation Coefficient

	Digital vs Analog Radiographs											
	DJD/10	DJD Yes/No	Osteophytes	JAM	Sclerosis	Effusion	Enthesophytes	Erosions–Cysts	IAM	Tarsal Fusion	Subluxation	Meniscal Mineralization
Elbow												
Kendall's τ	0.81	0.83	0.7	0.64	*	*	*	*				
P	< 0.0001	<0.0001	< 0.0001	<0.0001	—	—	—	—				
Tarsus												
Kendall's τ	0.63	0.57	0.54	0.59	*	1	0.14	*		0.54		
P	< 0.0001	<0.0001	< 0.0001	<0.0001	—	< 0.0001	0.11	—		< 0.0001		
Stifle												
Kendall's τ	0.88	0.89	0.65	—	*	*	1	*	0.89			0.84
P	< 0.0001	<0.0001	< 0.0001	0.6	—	—	< 0.0001	—	< 0.0001			< 0.0001
Coxofemoral												
Kendall's τ	0.42	0.26	0.57	*	*	*	*	*			0.26	
P	< 0.0001	0.003	< 0.0001	—	—	—	—	—			0.003	

*Insufficient number of affected joints to conduct a meaningful statistical analysis. *P*-values <0.05 indicate that correlation between digital and analog film radiographs is significant. Kendall's τ correlation coefficient results were interpreted as follows: 0, no or negative correlation; 0–0.2, slight correlation; 0.21–0.4, fair correlation; 0.41–0.6, moderate correlation; 0.61–0.8, substantial correlation; 0.81–1, almost perfect correlation; 1, perfect correlation. JAM, joint-associated mineralizations; IAM, intraarticular mineralizations.

TABLE 2. *P*-values from the Wilcoxon's Signed-Rank Test for Comparison of Sensitivity between Digital and Analog Radiographs for Detection of Radiographic Features Indicative of DJD

	Sensitivity of Digital vs Analog Radiographs											
	DJD/10	DJD Yes/No	Osteophytes	JAM	Sclerosis	Effusion	Enthesophytes	Erosions–Cysts	IAM	Tarsal Fusion	Subluxation	Meniscal Mineralization
Elbow	0.0098	0.37	0.0098	0.13	*	*	*	*				
Tarsus	< 0.001	0.01	0.1	0.12	*	*	0.3	*		< 0.001		
Stifle	0.02	*	0.37	1	*	0.12	*	*	0.82			0.65
Coxofemoral	0.001	0.13	0.01	*	*	*	*	*			0.58	

*Insufficient number of affected joints to conduct a meaningful statistical analysis. Significant *P*-values indicate that the digital radiographs were more sensitive; nonsignificant *P*-values indicate there was no difference in sensitivity between digital and analog films. JAM, joint-associated mineralizations; IAM, intraarticular mineralizations.

subchondral bone in two joints (8%). Joint effusion or subchondral erosions–cysts were not seen in any elbow.

Tarsal Joint

Thirty-four (57%) tarsal joints had radiographic DJD with a median subjective radiographic DJD score of 1 (range, 1–5). New bone formation on the dorsal surface of intertarsal and tarsometatarsal joints was detected in 26 joints (77% of joints with radiographic signs of DJD); enthesophytes in nine joints (27%); joint effusion and joint-associated mineralizations were identified in six joints each (18%); osteophytes in five joints (15%); subchondral bone sclerosis in two joints (6%); subchondral bone erosions–cysts in one joint (2.9%).

Stifle Joint

Thirty-nine (65%) of the 60 stifle joints had radiographic DJD with a median subjective radiographic DJD score of 1 (range, 1–5). Intraarticular mineralization was detected in 34 joints (87% of joints with radiographic signs of DJD), 32 of these were classified as meniscal mineralization; joint effusion in four joints (10%); osteophytes in three joints (8%); enthesophytes and joint-associated mineralizations in two joints each (5%); subchondral sclerosis and erosions–cysts were not detected in any stifle joint.

Coxofemoral Joint

Twenty-nine (49%) of the 59 coxofemoral joints had radiographic DJD with a median subjective radiographic DJD score of 2 (range, 1–8). Osteophytes were detected in 25 (86% of joints with radiographic signs of DJD), coxofemoral subluxation in 12 joints (41%), subchondral sclerosis and joint-associated mineralization in three joints each (10%). Joint-associated mineralization, joint effusion, enthesophytes, and subchondral erosions–cysts were not detected in any coxofemoral joint.

Based on India ink staining, macroscopic cartilage damage/fibrillation was present in 166 joints (69% of all the joints evaluated) with a median value of 2 (range, 1–4). Complete articular cartilage erosion with exposure of subchondral bone (Cartilage Damage Score 4) was present in 16 joints (7%).

Macroscopic Evaluation of Cartilage

Elbow Joint

Cartilage damage was present in 43 (72%) elbow joints. The elbow joints with cartilage damage had a median India ink score of 2 (range, 2–4) and a mean Total Cartilage Damage Score of 176 (± 149). Cartilage damage was seen most often on the ulna, in the area of the medial coronoid process, and on the corresponding medial humeral condyle. Of joints with cartilage damage, the mean Cartilage Damage $\text{Score}_{\text{humerus}}$ was 64 (± 59), the mean Cartilage Damage $\text{Score}_{\text{ulna}}$ was 71 (± 62), and the mean Cartilage Damage $\text{Score}_{\text{radius}}$ was 41 (± 42).

Tarsal Joint

Cartilage damage was present in 32 (53%) tarsal joints. The tarsal joints with cartilage damage had a median India ink score of 2 (range, 2–4) and a mean Total Cartilage Damage Score of 101 (± 133). Cartilage damage was seen on the trochlea of the talus and on the corresponding distal articular surface of the tibia. Of joints with cartilage damage, the mean Cartilage Damage $\text{Score}_{\text{tibia}}$ was 52 (± 70) and the mean Cartilage Damage $\text{Score}_{\text{talus}}$ was 49 (± 66).

Stifle Joint

Cartilage damage was present in 48 (80%) stifle joints. The stifle joints with cartilage damage had a median India ink score of 3 (range, 2–4) and a mean Total Cartilage Damage Score of 115 (± 97). Cartilage damage was located mainly on the patella and in the medial compartment of the joint, including the medial femoral condyle

and medial tibial condyle. The lateral femoral and tibial condyles were less affected. The mean Cartilage Damage $Score_{femur\ med\ condyle}$ was 36 (± 44), the mean Cartilage Damage $Score_{femur\ lat\ condyle}$ was 5 (± 8), the mean Cartilage Damage $Score_{femur\ trochlea}$ was 14 (± 20), the mean Cartilage Damage $Score_{tibia\ med\ condyle}$ was 17 (± 26), the mean Cartilage Damage $Score_{tibia\ lat\ condyle}$ was 3 (± 7), and the mean Cartilage Damage $Score_{patella}$ was 41 (± 41).

Coxofemoral Joint

Cartilage damage was present in 43 (73%) coxofemoral joints. The coxofemoral joints with detectable cartilage damage had a median India ink score of 2 (range, 2–4) and a mean Total Cartilage Damage Score of 101 (± 75). Most cartilage damage was located on the craniodorsal surface of the femoral head and on the corresponding surface on the acetabulum. The mean Cartilage Damage $Score_{femoral\ head}$ was 52 (± 40) and the mean Cartilage Damage $Score_{acetabulum}$ was 50 (± 42).

Considering the surfaces measured, and based on the mean percent cartilage damage, the joint with the greatest extent of cartilage damage was the elbow joint with a mean of 10.5% Total Cartilage Damage. The stifle joint was next most affected with a mean 7.6%, followed by the coxofemoral joint with a mean of 6%, and the tarsus with a mean of 4.4%.

Comparison of Macroscopic Cartilage Damage and Digital Radiographic Features

When considering all the joints, there was a significant correlation between the India ink retention score and the subjective radiographic DJD score as well as the radiographic evidence of osteophytes and joint-associated mineralizations (Table 3). The other radiographic signs of DJD that were common to all joints (enthesophytes, joint effusion, erosions–cysts, and sclerosis) were not present in enough joints to conduct a meaningful statistical analysis.

TABLE 3. Correlation Between Radiographic DJD Scores and India Ink Scores Using Kendall's τ Correlation Coefficient

	Digital Radiographic DJD Scores vs India Ink Scores		
	DJD/10	Osteophytes	JAM
Elbow	0.5 ($P<0.0001$)	0.52 ($P<0.0001$)	0.38 ($P<0.0001$)
Tarsus	0.26 ($P=0.003$)	0.35 ($P=0.0001$)	0.18 ($P=0.043$)
Stifle	0.28 ($P=0.001$)	0.17 ($P=0.055$)	0.14 ($P=0.12$)
Coxofemoral	0.42 ($P<0.0001$)	0.43 ($P<0.0001$)	0.23 ($P=0.009$)
All	0.35 ($P<0.0001$)	0.3 ($P<0.0001$)	0.26 ($P<0.0001$)

P-values <0.05 indicate that correlation between digital radiographic DJD scores and India ink retention scores is significant. Kendall's τ coefficient results were interpreted as follows: 0, no or negative correlation; 0–0.2, slight correlation; 0.21–0.4, fair correlation; 0.41–0.6, moderate correlation; 0.61–0.8, substantial correlation; 0.81–1, almost perfect correlation; 1, perfect correlation. DJD, degenerative joint disease; JAM, joint-associated mineralizations.

In the elbow joint, significant correlation was found between the India ink retention score and the subjective radiographic DJD score, osteophytes and the presence of joint-associated mineralizations (Table 3). Correlation was not significant between India ink retention score and the radiographic evidence of sclerosis ($P=0.7$) or enthesophytes ($P=0.14$). Radiographic features indicative of joint effusion and subchondral bone erosions/cysts were not present in enough joints to perform meaningful statistical analysis. The most significant correlation was between India ink retention score and osteophytes present on digital radiographs (Kendall's $\tau=0.52$, moderate correlation; $P<0.0001$). Twenty (57%) of the 35 elbow joints with no radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 2 (range, 2–3). Twenty-three (92%) of the 25 elbow joints with radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 3 (range, 2–4).

In the tarsal joint, significant correlation was found between the India ink retention score and the subjective radiographic DJD score and the radiographic evidence of osteophytes, joint-associated mineralizations (Table 3), sclerosis (Kendall's $\tau=0.33$; $P=0.0002$), joint effusion (Kendall's $\tau=0.27$; $P=0.002$), and enthesophytes (Kendall's $\tau=0.18$; $P=0.04$). The presence of new bone formation in the dorsal surface of intertarsal and tarsometatarsal joints was not correlated significantly with the India ink retention score ($P=0.24$). Radiographic evidence of subchondral bone erosions–cysts was not present in enough joints to conduct meaningful statistical analysis. The most significant correlation was between India ink retention score and osteophytes present on digital radiographs (Kendall's $\tau=0.35$, fair correlation; $P=0.0001$). Twelve (46%) of the 26 tarsal joints with no radiographically detectable DJD had macroscopic cartilage damage with an ink score of 2. Twenty (59%) of the 34 tarsal joints with radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 2 (range, 2–4).

In the stifle joint, significant correlation was found between the India ink retention score and the subjective radiographic DJD score (Kendall's $\tau=0.28$; $P=0.001$), intraarticular mineralizations (Kendall's $\tau=0.32$; $P=0.0003$), and meniscal mineralization (Kendall's $\tau=0.25$; $P=0.004$). No significant correlation was found between the India ink retention score and the radiographic evidence of osteophytes ($P=0.055$), joint-associated mineralizations ($P=0.12$), joint effusion ($P=0.3$), or enthesophytes ($P=0.12$). Sclerosis and subchondral bone erosions/cysts were not present in enough joints to conduct a meaningful statistical analysis. The most significant correlation was between India ink retention score and

intraarticular mineralization present on digital radiographs (Kendall's $\tau = 0.32$, fair correlation; $P = 0.0003$). Fifteen (71%) of the 21 stifle joints with no radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 2 (range, 2–3). Thirty-three (85%) of the 39 stifle joints with radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 3 (range, 2–4).

In the coxofemoral joint, significant correlation was found between the India ink retention score and the subjective radiographic DJD score, the radiographic evidence of osteophytes, joint-associated mineralizations (Table 3), and joint subluxation (Kendall's $\tau = 0.21$; $P = 0.017$). No significant correlation was found between the India ink retention score and the radiographic evidence of sclerosis ($P = 0.2$). The presence of joint effusion, enthesophytes, and subchondral bone erosions/cysts were not present in enough joints to conduct meaningful statistical analysis. The most significant correlation was between India ink retention score and osteophytes present on digital radiographs (Kendall's $\tau = 0.43$, moderate correlation; $P < 0.0001$). Seventeen (57%) of the 30 coxofemoral joints with no radiographically detectable DJD had macroscopic cartilage damage with an India ink score of 2. Twenty-six (90%) of the 29 coxofemoral joints with radiographically detectable DJD had macroscopic cartilage damage with a median India ink score of 2 (range, 2–4).

A positive value for mean (± SD) Total Cartilage Damage Score for those joints with subjective radiographic DJD scored as 0 indicated that cartilage damage was present without radiographic evidence of DJD. For joints with subjective DJD scored as 0, the elbow had a mean Total Cartilage Damage Score of 56 (± 75) ($N = 35$; $P < 0.0001$), the tarsus had a mean Total Cartilage Damage Score of 27 (± 57) ($N = 26$; $P = 0.008$), the stifle had a mean Total Cartilage Damage Score of 45 (± 61) ($N = 21$; $P = 0.0004$), and the coxofemoral joint had a mean Total Cartilage Damage Score of 49 (± 59) ($N = 30$; $P < 0.0001$).

Based on multiple linear regression analysis, the Total Cartilage Damage Score was best predicted by osteophytosis and age for the elbow ($r^2 = 0.51$); sclerosis and age for the tarsus ($r^2 = 0.82$); osteophytosis, subjective radiographic DJD score, intraarticular mineralizations and age for the stifle ($r^2 = 0.72$); and subluxation and age for the coxofemoral joint ($r^2 = 0.62$).

As there were many joints with Total Cartilage Damage Scores of zero, multiple linear regression was repeated using a two-step regression model. First a logistic regression was performed to determine the probability of scores being nonzero; then given that the scores were nonzero a linear regression was used. The two-step regression model produced a best-fit model very similar to the previously described model; it included the same factors in the coxofemoral joint, did not include age in the elbow joint and the tarsal joint, and it included meniscal mineralization as a new variable in the stifle joint.

DISCUSSION

We defined a list of radiographic features considered indicative of feline DJD, based on the radiographic changes that are identified in joint degeneration of other species. This was necessary because the radiographic features of feline DJD were undefined. It could be argued that some of the radiographic features scored in this study have not been proven to be secondary to joint degeneration or part of the degenerative process, such as dorsal new bone on the intertarsal and tarsometatarsal joints, joint-associated mineralizations or meniscal mineralization. For example, it has been suggested that periarticular soft tissue mineralization may not represent DJD.[1] However, meniscal mineralization is strongly associated with medial compartment stifle DJD.[19] Our data suggests that other poorly defined radiographic features, such as joint-associated mineralizations, may also be associated with joint degeneration.

Digital radiographs were equally or more sensitive for detection of degenerative changes vs. analog radiographs. This study was not designed to describe the sensitivity of digital radiographs for the detection of changes indicative of feline DJD but to determine which of the two systems was more sensitive. Given the superior dynamic range afforded by digital radiographs, it is not surprising that the digitally acquired images had similar or, for some radiographic changes, higher sensitivity than analog radiographs, even though analog radiographs have increased spatial resolution. As a result, digital radiographic data were used in the study.

The most common radiographic features of DJD were joint-associated mineralizations for the elbow joint, tarsometatarsal dorsal bone proliferation, intraarticular mineralizations in the stifle joint and osteophytes in the coxofemoral joint. Also, intraarticular opacity consistent with joint effusion and subchondral bone erosions–cysts were not detected often in feline joints, including those with severe cartilage damage and subchondral bone exposure. Except for the coxofemoral joint, osteophytes were not the most common radiographic sign of DJD, and their severity scores were low. Since other forms of new bone formation and joint-associated and intraarticular mineralizations were seen commonly in feline joints with DJD, the sentiment that cats form less new bone in association with DJD than other species should be clarified. Based on our results, cats form periarticular new bone, but the radiographic appearance is different to dogs. The fact that some radiographic features not commonly seen in dogs, such as joint-associated mineralizations and meniscal mineralization, were seen commonly in cats, suggests

that the radiographic signs of DJD are different in cats than dogs. This needs further clarification.

Imaging of cartilage using radiography is impossible since cartilage silhouettes with joint fluid and cannot be distinguished unless mineralized. Thus, the conventional radiographic evaluation of DJD is based on the presence of other radiographic changes that are related with joint degeneration. Although conventional radiographs are the easiest indirect method to evaluate degenerative changes in joints, little is known about the usefulness of the radiographic features of osteoarthritis as predictors of articular cartilage degeneration in humans or animals. Marginal osteophytes were the most sensitive radiographic feature for detection of osteoarthritis of the tibiofemoral joint in people.[14] Our results indicate that when considering all joints, there is significant correlation between cartilage damage and the detection of osteophytes and joint-associated mineralizations. However, these results should interpreted cautiously since this correlation was only fair (Kendall's $\tau = 0.21$–0.4). When looking at the various joints individually, although most of the correlations were statistically significant, only the presence of osteophytes and the subjective radiographic DJD score had a correlation above 0.4 (moderate correlation) with the presence of cartilage damage in the elbow and coxofemoral joints. The correlation of cartilage damage with the other radiographic features was either fair to moderate, or not significant. This resulted from the high numbers of joints with no radiographic signs of DJD, but with cartilage lesions present.

Cautious interpretation should also be made about the insignificant correlation between India ink retention and radiographic dorsal new intertarsal and tarsometatarsal bone. In this study, as an initial evaluation, the talocrural, tarsometatarsal, and intertarsal joints were considered as a single entity when evaluating radiographic signs of DJD. However, cartilage damage was evaluated only in the main and more mobile talocrural joint and not in any of the intertarsal or tarsometatarsal joints. This likely explains the reason why the correlation between ink retention score and the presence of new bone formation in the intertarsal and tarsometatarsal joints was not significant and the same could explain the significant but slight correlation (Kendall's $\tau = 0.26$; $P = 0.003$) between ink score and the subjective radiographic DJD score in the tarsal joint. However, the study was designed to evaluate the radiographic features of the whole joint, but to evaluate the cartilage only in the most mobile aspect of the joint. That the dorsal new bone does not correlate with cartilage damage in the tibio-tarsal joint is clinically relevant.

It may be possible to detect various degrees of cartilage damage radiographically using diffraction enhanced radiographic imaging.[20,21] High-resolution magnetic resonance imaging (at 4 T) and micro-CT can also be used to detect cartilage lesions with a diameter >2 mm, but their ability to detect fibrillation, surface irregularities, and cracks was poor in other studies.[22]

It is not surprising that cartilage fibrillation was present in some joints before evidence of DJD was apparent radiographically. Cartilage damage is an early change in the process of joint degeneration and other changes, such as osteophytosis and subchondral sclerosis, become apparent radiographically only in more advanced stages of the disease. However, based on what we observed, severe cartilage damage with exposure of subchondral bone may be present with only mild radiographic evidence of DJD.

There may be a mismatch between radiographic changes of DJD and pain elicited on joint manipulation. For example, in one evaluation, 34% of painful joints did not have radiographic evidence of DJD.[3] And, in another comparison, only 33% of joints with radiographic signs of DJD were painful on manipulation.[8] Difficulty in assessing pain in cats may be the cause of this mismatch. Based on our results, the presence of moderate and severe cartilage damage in joints with normal radiographs or mild radiographic signs of DJD may explain this mismatch partially.

The greatest cartilage damage was seen in the elbow and stifle joints, with the distribution of the lesions being consistent with medial compartment disease. In other work, we found radiographic evidence of meniscal mineralization as a predictor of medial compartment stifle joint disease.[19] This has also been suggested in guinea-pigs.[23]

Medial compartment elbow joint disease is recognized in dogs[24,25] and appears to be associated with medial coronoid process disease, humeroulnar incongruency, and abnormal forces acting in the medial compartment of the joint.[26–28] The cause of cartilage damage in the medial compartment of the elbow joints in this study is unknown. Fragmented medial coronoid process or elbow incongruency have not been reported in cats, although arthroscopically detected craniomedial elbow fragments in a cat were suggested to be from the medial coronoid process. [29] In our study, intraarticular osteochrondral fragments were found in some elbows with cartilage damage of the medial compartment, but the medial coronoid process was macroscopically assessed to be intact in those joints. We did not determine the cause of medial compartment cartilage damage of the feline elbow joint observed herein.

The determination of the Total Cartilage Damage Score and the Cartilage Damage Score was based on calculating the fraction of the total articular cartilage that was damaged from digital photographs. Despite the fact that the surfaces being measured were curved, the decision was made to use digital photographs rather than tracings from superimposed thin plastic film.‖ Tracings were inaccurate because the thin plastic could not be adapted accurately to the small articular surfaces and it was difficult to identify

‖Parafilm: Pechiney Plastic Packaging Company, Chicago, IL.

the lesions through the plastic. Digital photographs were made at the same distance and same exact position to minimize variance.

Therefore, based on our results, we reject the null hypothesis that there is no correlation between radiographic features of DJD and the presence of macroscopically detectable articular cartilage damage in feline appendicular joints. However, there were only fair to moderate correlations between radiographic features of DJD and the presence of macroscopic cartilage damage. The joint most likely to have cartilage damage without radiographic evidence of DJD is the stifle (71%) followed by the coxofemoral joint (57%), elbow (57%), and tarsal joint (46%). The digital radiographic findings indicative of DJD with the greatest association with cartilage damage were the presence of osteophytes for the elbow (Kendall's $\tau = 0.52$, moderate correlation; $P < 0.0001$), tarsal (Kendall's $\tau = 0.35$, fair correlation; $P = 0.0001$), coxofemoral joints (Kendall's $\tau = 0.43$, moderate correlation; $P < 0.0001$), and intraarticular mineralizations for the stifle joint (Kendall's $\tau = 0.32$, fair correlation; $P = 0.0003$).

ACKNOWLEDGMENTS

This study was funded by Novartis Animal Health, through their competitive grants program. The authors have no financial or personal relationships that could possibly influence or inappropriately bias this work.

REFERENCES

1. Clarke SP, Mellor D, Clements DN, et al. Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. Vet Rec 2005;157:793–799.

2. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). J Am Vet Med Assoc 2002;220:628–632.

3. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study of 28 cases. J Small Anim Pract 2006;47:439–445.

4. Godfrey DR. Osteoarthritis in cats: a retrospective radiological study. J Small Anim Pract 2005;46:425–429.

5. Lascelles BD, Henry JB, Brown J, et al. Cross-sectional study evaluating the prevalence of radiographic degenerative joint disease in domesticated cats. Vet Surg 2010;39:535–544.

6. Lascelles BD. Feline degenerative joint disease. Vet Surg 2010;39:2–13.

7. Gunew MN, Menrath VH, Marshall RD. Long-term safety, efficacy and palatability of oral meloxicam at 0.01–0.03 mg/kg for treatment of osteoarthritic pain in cats. J Feline Med Surg 2008;10:235–241.

8. Lascelles BD, Hansen BD, Roe S, et al. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. J Vet Intern Med 2007;21:410–416.

9. Lascelles BD, Depuy V, Thomson A, et al. Evaluation of a therapeutic diet for feline degenerative joint disease. J Vet Intern Med 2010; 24:487–495.

10. Allan GS. Radiographic features of feline joint diseases. Vet Clin N Am Small Anim Pract 2000;30:281–302.

11. Lascelles BD, Henderson AJ, Hackett IJ. Evaluation of the clinical efficacy of meloxicam in cats with painful locomotor disorders. J Small Anim Pract 2001;42:587–593.

12. Bennett D, Morton C. A study of owner observed behavioural and lifestyle changes in cats with musculoskeletal disease before and after analgesic therapy. J Feline Med Surg 2009;11:997–1004.

13. Kijowski R, Blankenbaker DG, Stanton PT, Fine JP, De Smet AA. Radiographic findings of osteoarthritis versus arthroscopic findings of articular cartilage degeneration in the tibiofemoral joint. Radiology 2006;239:818–824.

14. Kijowski R, Blankenbaker D, Stanton P, Fine J, De Smet A. Correlation between radiographic findings of osteoarthritis and arthroscopic findings of articular cartilage degeneration within the patellofemoral joint. Skeletal Radiol 2006;35:895–902.

15. Bushberg JT, Seibert JA, Leidholdt EM Jr, Boone JM. Digital radiography. In Wilkins LW (ed): The Essential Physics of Medical Imaging. Philadelphia: Williams & Wilkins, 2002;293–316.

16. Cake MA, Read RA, Guillou B, Ghosh P. Modification of articular cartilage and subchondral bone pathology in an ovine meniscectomy model of osteoarthritis by avocado and soya unsaponifiables (ASU). Osteoarthritis Cartilage 2000;8:404–411.

17. Meachim G. Light microscopy of Indian ink preparations of fibrillated cartilage. Ann Rheum Dis 1972;31:457–464.

18. Yoshioka M, Coutts RD, Amiel D, Hacker SA. Characterization of a model of osteoarthritis in the rabbit knee. Osteoarthritis Cartilage 1996;4:87–98.

19. Freire M, Brown J, Robertson ID, et al. Meniscal mineralization in domestic cats. Vet Surg 2010;39:545–552.

20. Muehleman C, Li J, Zhong Z. Preliminary study on diffraction enhanced radiographic imaging for a canine model of cartilage damage. Osteoarthritis Cartilage 2006;14:882–888.

21. Muehleman C, Chapman LD, Kuettner KE, et al. Radiography of rabbit articular cartilage with diffraction-enhanced imaging. Anat Rec A Discov Mol Cell Evol Biol 2003;272:392–397.

22. Batiste DL, Kirkley A, Laverty S, et al. High-resolution MRI and micro-CT in an ex vivo rabbit anterior cruciate ligament transection model of osteoarthritis. Osteoarthritis Cartilage 2004;12: 614–626.

23. Kapadia RD, Badger AM, Levin JM, et al. Meniscal ossification in spontaneous osteoarthritis in the guinea-pig. Osteoarthritis Cartilage 2000;8:374–377.

24. Fitzpatrick N, Yeadon R. Working algorithm for treatment decision making for developmental disease of the medial compartment of the elbow in dogs. Vet Surg 2009;38:285–300.

25. Fitzpatrick N, Yeadon R, Smith T, Schulz K. Techniques of application and initial clinical experience with sliding humeral osteotomy for treatment of medial compartment disease of the canine elbow. Vet Surg 2009;38:261–278.

26. Ness MG. Treatment of fragmented coronoid process in young dogs by proximal ulnar osteotomy. J Small Anim Pract 1998;39: 15–18.

27. Fitzpatrick N, Smith TJ, Evans RB, Yeadon R. Radiographic and arthroscopic findings in the elbow joints of 263 dogs with medial coronoid disease. Vet Surg 2009;38:213–223.

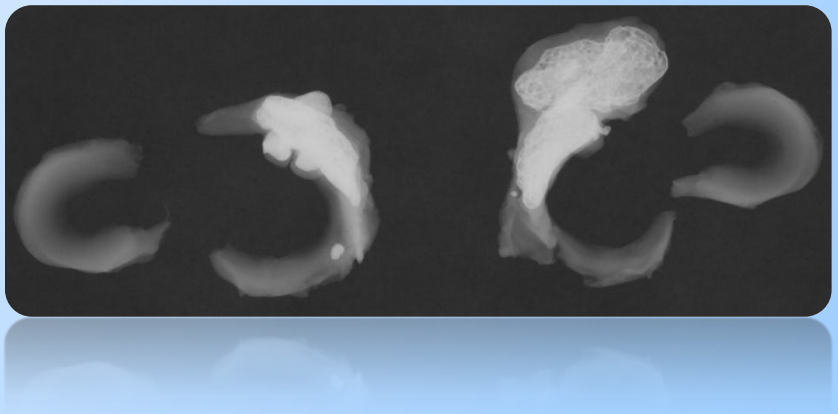
28. Kirberger RM, Fourie SL. Elbow dysplasia in the dog: pathophysiology, diagnosis and control. J S Afr Vet Assoc 1998;69:43–54.

29. Staiger BA, Beale BS. Use of arthroscopy for debridement of the elbow joint in cats. J Am Vet Med Assoc 2005;226:401–403.

PUBLICATION 3

Meniscal Mineralization in Domestic Cats. Freire M, Brown J, Robertson ID, Pease AP, Hash J, Hunter S, Simpson W, Thomson Sumrell A, Lascelles BD. *Veterinary Surgery*. 2010;39(5):545-52.

http://www.ncbi.nlm.nih.gov/pubmed/20345540



Meniscal Mineralization in Domestic Cats

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Submitted May 2009; Accepted August 2009

DOI:10.1111/j.1532-950X.2010.00648.x

Objective: To (1) determine prevalence of radiographically detectable meniscal mineralization in domestic cats and (2) to evaluate the association between meniscal mineralization and degenerative joint disease (DJD).
Study Design: Prospective study.
Animals: Client-owned cats (n = 100) and 30 feline cadavers.
Methods: Randomly selected client-owned cats were used to determine the prevalence of meniscal mineralization. Stifles from feline cadavers were used to evaluate the relationship between meniscal mineralization (using high-resolution X-ray), radiographic DJD, and cartilage damage. Menisci were evaluated histologically.
Results: Forty-six percent of the client-owned cats had meniscal mineralization detected in 1 or both stifles. Pain scores were not significantly different between stifles with meniscal mineralization and those with no radiographic pathology ($P = .38$). Thirty-four of 57 cadaver stifles had meniscal mineralization, which was always located in the cranial horn of the medial meniscus. Percentage mineralization of the menisci was significantly correlated with the cartilage damage score of the medial femoral ($r^2 = 0.6$; $P < .0001$) and tibial ($r^2 = 0.5$; $P < .0001$) condyles as well as with the total joint cartilage damage ($r^2 = 0.36$; $P < .0001$) score and DJD score ($r^2 = 0.8$; $P < .0001$).
Conclusion: Meniscal mineralization is a common condition in domestic cats and seems to indicate medial compartment DJD.
Clinical Relevance: Clinical significance of meniscal mineralization is uncertain. Further work is needed to determine if the meniscal mineralization is a cause, or a consequence of joint degeneration.

Meniscal mineralization is a poorly understood condition that has been reported in reptiles, rodents, birds, nondomestic cats, and nonhuman primates.[1–4] Although described in people, it is considered a rare condition[5–12] and there have been a few case reports in dogs and domestic cats.[1,13,14]

The cause of meniscal mineralization (meniscal ossification[1,2,11–15]; meniscal ossicles[6–11,16]; meniscal calcification[1,5,13]) is unknown. Developmental (phylogenetic) and posttraumatic causes have been suggested in people.[6,7,10,12] The phylogenetic theory suggests that meniscal mineralization represents a congenital vestigial structure that should be interpreted as a variant of normal anatomy.[6,7] The posttraumatic theory asserts that meniscal mineralization is acquired by degeneration or metaplasia after isolated or recurrent trauma.[7] It has been suggested that meniscal mineralization is a normal anatomic feature in nondomestic cats,[2] a primary vestigial anomaly in dogs and cats,[1,14] and to occur secondary to trauma or in association with cranial cruciate ligament rupture in dogs and cats.[1,13]

The frequency of occurrence of meniscal mineralization in domestic cats is unknown. It is also unknown if meniscal mineralization is associated with joint pain or lameness or if meniscal mineralization is associated with degeneration of joint tissues such as cartilage.

Our purpose was to determine prevalence of radiographically detectable meniscal mineralization in domestic cats. We hypothesized that the prevalence was high ($> 30\%$) and further, that meniscal mineralization is

Study was funded by a grant from Novartis Animal Health through their global Fellowship Research Program

associated with degenerative joint disease (DJD), as indicated by cartilage degeneration.

MATERIALS AND METHODS

We conducted a prospective, observational study. Part I established the prevalence of radiographically detectable meniscal mineralization in domestic cats and part II evaluated the relationship between meniscal mineralization and DJD measured by cartilage damage.

Cats

Prevalence Study. A population of 100 client-owned cats randomly selected from the client database of Morrisville Cat Hospital (Morrisville, NC) was used to determine the prevalence of radiographically detectable meniscal mineralization.

Cadaver Study. Thirty adult cats euthanatized (population control) at a county animal shelter were studied. We aimed to recruit 30 cats of any age, equally distributed between cases with and without radiographically detectable meniscal mineralization, with no other detectable stifle pathology.

Prevalence Study

Using a database of 1640 cats from a single veterinary practice, a population of 100 cats was randomly selected for study. To achieve this, the cats in the database were divided into 4 age groups (0–5; 5–10; 10–15; and 15–20 years old). Cats that were exactly 5, 10, or 15 years old were assigned to the 6 months–5 years, 5–10 years, and 10–15 years groups, respectively. Within each age group, each cat was assigned a unique number, and then the cats in each group were randomly ranked using computer software. The first 25 cats in each group whose owners were willing to participate in the study were included. Once selected, each cat was evaluated, sedated, and orthogonal radiographic projections of the stifle joints taken using an indirect digital flat panel imaging system (Canon Medical CXDI-50G Sensor, Eklin Medical Systems, Santa Clara, CA).

Digital radiographs made were evaluated by 2 board certified radiologists (A.P., J.B.) and a board certified surgeon (B.D.X.L.) for radiographically detectable pathology including meniscal mineralization. Digital radiographs were viewed (Dell Ultra-sharp 2407WFP color monitors, 24'' LCD resolution of 1920×1200) and standard medical image viewing software (eFilm 2.1.2, Merge Healthcare, Milwaukee, WI). Radiologic features considered indicative of presence of DJD were: joint effusion, osteophytes, enthesiophytes, joint associated mineralization, sclerosis, subchondral bone erosions-cysts, and presence of intra-articular mineralizations. Meniscal mineralization was considered under intra-articular mineralization as a mineralization detected in the intra-articular space, and which appeared to be located within the area of the lateral or medial menisci in both craniocaudal and mediolateral projections of the stifle (Fig 1). A scale (0–4) was used for grading of severity of each of the radiographic changes identified (0 = normal; 1 = trivial; 2 = mild; 3 = moderate; 4 = severe). A subjective radiographic DJD score (0–10) where 0 = no radiographic abnormalities identified and 10 = ankylosis, was assigned to each stifle based on the presence of radiographic change and its severity. Age, weight, body condition score (BCS; http://www.ivis.org/journals/vetfocus/16_1/en/7.pdf), breed, and sex of the cats were recorded. During orthopedic evaluation, the response to

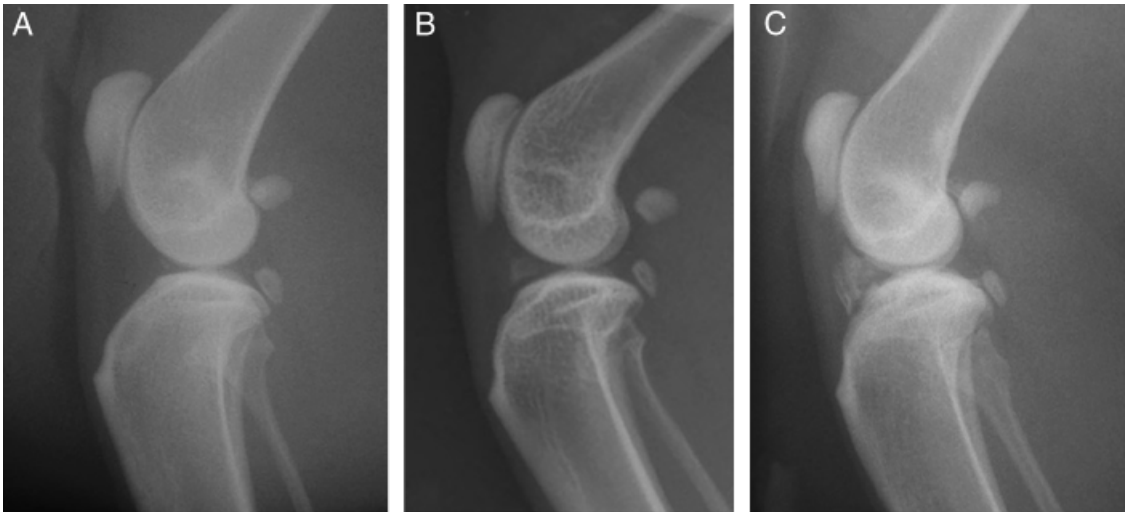


Figure 1 The severity of radiographically detectable meniscal mineralization was graded using a scale from 0–4 (0 = normal; 1 = trivial; 2 = mild; 3 = moderate; 4 = severe). The stifle digital radiographs from cadaver specimens show meniscal mineralizations graded as trivial (A), moderate (B), and severe (C).

palpation of every joint and part of the axial skeleton was graded: 0 = no resentment; 1 = mild withdrawal, mildly resists; 2 = moderate withdrawal, body tenses, may orient to site, may vocalize, increase in vocalization; 3 = orients to site, forcible withdrawal from manipulation, may vocalize or hiss or bite; and 4 = tries to escape, prevent manipulation, bite/hiss, marked guarding of area.

Cadaver Study

After euthanasia, body weight and BCS were recorded and an orthopedic examination of each stifle joint was performed. Only cats without grossly detectable stifle pathology (cranial cruciate ligament rupture, patella luxation) were included in the study. The presence of grade I patella luxation was considered acceptable. Orthogonal radiographs of the cadaver stifle joints were acquired using a digital imaging system (described above) and also with a high detail film/screen system (Kodak Lanex Fine screens, Carestream Health, Rochester, NY; Super HR-U $\times$ 30 ray film, Fuji Medical Systems, Stamford, CT). Both digital and analog radiographs were evaluated blindly by the same board certified veterinary radiologists and surgeon to determine radiographic scores based on the features described earlier.

Morphologic Examination. Stifle joints were carefully opened to avoid damage to any cartilage surfaces for gross observation. Menisci were dissected from their attachments and retained for evaluation. The surface appearance of the joints was studied for fibrillation and/or erosion of the articular cartilage using India ink application.[17] The cartilage surface was painted with India ink twice, rinsing the cartilage with water each time, 3 minutes after the ink was applied. The severity of surface damage of the articular cartilage was scored based on ink retention, and graded[18]: grade 1 = intact surface: surface appears normal and does not retain any ink; grade 2 = minimal fibrillation: site appears normal before staining, but retains India ink as elongated specks or light gray patches; grade 3 = overt fibrillation: the cartilage is velvety in appearance and retains ink as intense black patches; and grade 4 = erosion: loss of cartilage exposing the underlying bone.

The severity of articular cartilage damage present in each stifle joint was expressed as the total cartilage damage score (TCDS) calculated from the addition of the cartilage damage score (CDS) of 6 articular areas: medial and lateral femoral condyles, medial, and lateral tibial condyles, patella and femoral trochlea. CDS of each of those areas was calculated as the percent of the total articular cartilage area damaged, multiplied by the degree of cartilage damage based on the ink retention grading system. CDS value ranged from 0 to 400 (0 = no cartilage damage; 400 = complete exposure of subchondral bone over the whole of the articular surface of that bone). TCDS and CDS were calculated using the following equations:

$$\mathrm{CDS} = [\%\mathrm{area}_1 \times \mathrm{ink\ grade}_{\mathrm{area1}}] + [\%\mathrm{area}_2 \times \mathrm{ink\ grade}_{\mathrm{area2}}]$$

$$\begin{aligned}\mathrm{TCDS} = {} & \mathrm{CDS}_{\mathrm{lat\ fem\ condyle}} + \mathrm{CDS}_{\mathrm{med\ fem\ condyle}} \\ & + \mathrm{CDS}_{\mathrm{lat\ tibial\ condyle}} + \mathrm{CDS}_{\mathrm{med\ tibial\ condyle}} \\ & + \mathrm{CDS}_{\mathrm{patella}} + \mathrm{CDS}_{\mathrm{femoral\ trochlea}}\end{aligned}$$

TCDS value ranged from 0 to 2400 (0 = no cartilage damage present; 2400 = complete exposure of subchondral bone over all articular surfaces).

To calculate CDS and TCDS, digital photographs of the femoral condyles, femoral trochlea, tibial plateau, and patella, after the application of the India ink, were made by photographing these surfaces in exactly the same way each time. Computer software (Adobe Photoshop 7.0, Adobe, San Jose, CA) was used to calculate the percent of the cartilage area retaining India ink as a result of cartilage fibrillation. Despite the fact that some of the surfaces being measured were curved, pilot work established that the use of X-ray film or thin plastic compared with digital photographs to measure damaged areas resulted in significantly greater variance, and small areas of cartilage damage were difficult to define through the plastic.

Imaging. High detail radiographs (Faxitron X-Ray system, Fuji Medical X-Ray Film; Super HR-U 30; Fujifilm; Stamford, CT; 30 kV, 40 seconds) of menisci from the stifle joints were evaluated looking for presence of meniscal mineralization. Location and number of discrete areas of mineralization were described. High detail radiographic images were digitized (1.5″ by 3″ radiographs photographed using Nikon D2$\times$ 10MP 35 mm digital camera, producing images of 4288 $\times$ 2848 pixels) and using computer software (Adobe Photoshop 7.0) the calcified area of the meniscus was calculated and expressed as a percent of the total area of the meniscus ($\%\mathrm{Min}_{\mathrm{FAX}}$).

Microscopy. Harvested menisci were fixed in 10% formalin for 48 hours. Menisci that could not be cut were decalcified in formic acid solution for 24–48 hours. After fixation and decalcification, menisci were divided into 3 with 2 cuts oriented radially to the peripheral margin of the meniscus, creating cranial, middle, and caudal sections. Meniscal segments were sectioned, stained with hematoxylin and eosin and evaluated histologically. In every case with radiographically detectable mineralization, sectioning was continued until the area of mineralization was identified histologically.

Statistical Analysis

Descriptive statistics were used to describe the prevalence of meniscal mineralization in the clinical population. Cats with no radiographic stifle pathology and those with only meniscal mineralization were compared for age, weight, BCS, and sex of cat, using t-tests, χ^2-tests, and Kruskal–Wallis tests. Individual stifles with no radiographic stifle pathology and those with only meniscal

mineralization were compared for pain on manipulation using a Kruskal–Wallis test.

For the cadaver study, using $\%Min_{FAX}$ as the gold standard for the detection of meniscal mineralization, the sensitivity and specificity of digital and (traditional) analog high-detail film/screen radiographs were calculated. Subjective total DJD scores between stifles with and without meniscal mineralization were compared using the Kruskal–Wallis test. Nonpaired t-tests were used to compare TCDS and CDS between stifles with and without meniscal mineralization. A correlation coefficient was calculated to describe the relationship between the $\%Min_{FAX}$ and CDS and TCDS of the joint surfaces, as well as with the subjective total DJD score. Values of $P < .05$ were considered significant.

RESULTS

Prevalence Study

Twenty-five cats in each age group were successfully recruited and studied; 18 were pure-bred and 82 were domestic short or long hair. There were 40 male castrated (MC) and 60 female spayed (FS). Mean ($\pm$SD) age was 9.42 ± 5.05 years and mean weight was 5.12 ± 1.63 kg (range, 2.08–10.16 kg).

Forty-six cats had meniscal mineralization detected in one or both stifles (27 cats bilateral, 19 cats unilateral). In those cats with unilateral meniscal mineralization, the right stifle was affected in 10 and the left stifle in 9 cats. Cats with meniscal mineralization were 17 castrated males and 29 spayed females with a mean age of 10.70 ± 4.73 years and mean weight of 4.92 ± 1.57 kg. Fifty-four cats (54%; 17 castrated males, 31 spayed females; mean age, 8.33 ± 5.13 years; mean weight, 5.80 ± 1.7 kg) had no meniscal mineralization detected on digital radiographs. Of 100 cats evaluated, 21 (21%) had meniscal mineralization as the only radiographic change detected on digital radiographs of the stifles, and 36 cats (36%) had no radiographic signs indicative of any stifle pathology. Cats with meniscal mineralization were significantly older (10.50 ± 5.2 years; $P = .027$), weighed significantly less (4.57 ± 1.46 kg; $P = .043$) and were of significantly lower BCS (median, 2; range, 1–5; $P = .039$) than those with no radiographic stifle pathology (age, 7.46 ± 4.64 years; weight, 5.50 ± 1.71 kg; median BCS, 3 [range, 2–5]).

Of 200 stifles evaluated, 73 (37%) had meniscal mineralization identified on digital radiographs. Of the affected stifles, 54 (27% of all stifles) had no other radiographic signs of DJD besides meniscal mineralization. There was no significant difference between the pain scores for stifles with no radiographic pathology and those with only meniscal mineralization ($P = .38$).

Cadaver Study

Of 30 cats, 3 stifles were excluded: 1 because intra-articular mineralization other than meniscal mineralization was identified in both stifles (the origin of those mineralizations could not be determined on macroscopic examination) and 1 cat had a cranial cruciate ligament rupture in the right stifle. Thus, 57 stifles from 29 cats were included in the analysis. Breeds were domestic short hair (23), domestic medium hair (2), domestic long hair (2), Main Coon (1), and Himalayan (1). There were 6 spayed females, 13 females, 8 castrated males, and 2 males. Mean ($\pm$SD) age of the cats was 9.91 ± 4.61 years, mean weight was 4.8 ± 1.33 kg, and median BCS was 3 (range, 2–5). No significant differences were found in age ($P = .15$), weight ($P = .44$), and BCS ($P = .61$) between cats with and without meniscal mineralization.

Meniscal mineralization was detected on high detail radiographs of medial and lateral menisci in 34 of 57 stifles (60%). Mineralization was located in the cranial horn of the medial meniscus in all instances and partially involved the cranial intermeniscal ligament in 3 stifles. Sixteen cats had bilateral (left and right stifle medial meniscus) mineralization, 1 cat had unilateral meniscal mineralization, 1 cat had bilateral meniscal mineralization but the right stifle was not included because of cranial cruciate ligament rupture, and 11 cats had no meniscal mineralization in either stifle. Mineralization was confined to a single area in 13 (38%) menisci and multiple areas in 21 (62%) menisci. In menisci with mineralization, $\%Min_{FAX}$ had a mean ($\pm$SD) value of $7.83 \pm 11.22\%$ of the total area of the meniscus (range, 1.5–55%; Fig 2). Digital radiographs had a

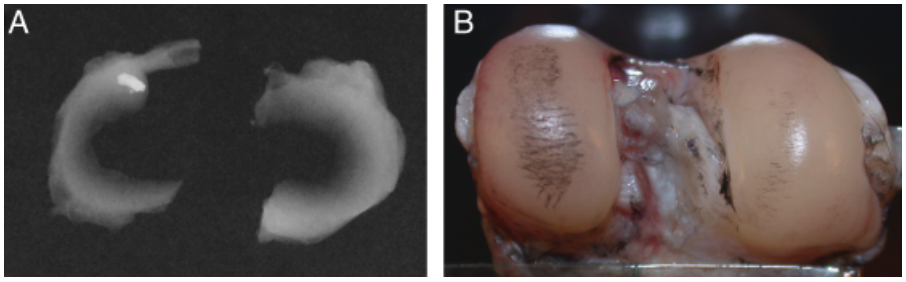


Figure 2 Mineralization of the cranial horn of the medial meniscus (left) on a cadaver specimen detected on high detail (Faxitron) radiographs (A) Severity of meniscal mineralization based on digital radiographs of this cadaver specimen was graded as trivial. Articular surface of the distal femur of the same specimen shows the difference in cartilage fibrillation and erosion of the medial (left) and lateral (right) femoral condyles after the application of India ink (B).

sensitivity and specificity of 91% and 100%, respectively, for detection of meniscal mineralization. Analog high detail film/screen radiographs had a sensitivity and specificity of 88% and 100%, respectively, for detection of meniscal mineralization.

Significant differences were found for subjective total DJD scores assigned from digital (median 1; range 0–5) and analog high detail film/screen radiographs (median 1; range 0–4; $P = .021$). The largest paired difference was 1, occurring in 8 of 57 stifles and in 3 stifles a score of 0 was assigned for the analog films, and 1 for the digital images. The subjective total DJD score from digital images was significantly different between stifles with meniscal mineralization (median, 1; range, 0–5) and without meniscal mineralization (median, 0; range, 0–1; $P < .001$).

Gross Morphologic Findings

The TCDS of the 57 stifles evaluated had a mean ($\pm$SD) value of 51 ± 92. CDS mean value for the 6 articular surfaces in the stifle joint were: medial femoral condyle 27 ± 42; lateral femoral condyle 3.8 ± 7.5; femoral trochlea 8.7 ± 15; medial tibial condyle 12 ± 24; lateral tibial condyle 2.6 ± 5.7; and patella 27 ± 32. The Ink score representing the worse cartilage damage in each stifle joint had a median value of 2 (range, 1–4). The TCDS was significantly different between stifles with meniscal mineralization (104 ± 103) and stifles without meniscal mineralization (50.5 ± 62.2; $P = .028$).

In stifles with mineralization of the menisci, CDS was significantly different when comparing medial (40.4 ± 48.9) and lateral (3.91 ± 6.33) femoral condyles ($P = .0001$), and medial (15.5 ± 29.0) and lateral (2.81 ± 6.42) tibial condyles ($P = .01$). In stifles without meniscal mineralization no significant differences were found in CDS when comparing medial (8.97 ± 16.8) and lateral (3.80 ± 9.05) femoral condyles ($P = .22$); however, CDS was significantly different for medial (8.70 ± 12.6) and lateral (2.21 ± 4.39) tibial condyles ($P = .009$).

Meniscal Mineralization and CDS Correlation

The percent area of the menisci taken up by the meniscal mineralization was significantly correlated with the CDS of medial femoral and medial tibial condyles as well as with the TCDS and subjective total DJD score ($P < .05$). This correlation was good with the medial femoral condyle ($r^2 = 0.6$; $P < .0001$), moderate with the medial tibial condyle ($r^2 = 0.5$; $P < .0001$), fair with the TCDS ($r^2 = 0.36$; $P < .0001$) and very good with the subjective total DJD score ($r^2 = 0.8$; $P < .0001$). No significant correlation was found between the percent of the menisci taken up by the meniscal mineralization and the CDS of the lateral femoral or tibial condyles, patella or femoral trochlea ($P > .05$).

Meniscal Histopathology

Meniscal mineralization was identified histologically in all the menisci in which mineralization was detected on high detail radiographs. Histopathologically, 14 menisci (41% of all the mineralized menisci), had intrameniscal ossification consisting of cancellous bone and bone marrow structure, and metaplasia of the fibrocartilage surrounding the ossified area (Fig 3). Twenty menisci (59% of all the mineralized menisci) showed intrameniscal mineralizations consisting of areas of chondro-osseous metaplasia of the fibrocartilage with no organized structure. No abnormalities were detected histopathologically in any of the lateral menisci (Fig 3).

DISCUSSION

Our results indicate that meniscal mineralization is a common feature detected on conventional orthogonal radiographs of the stifle in domestic cats. In a population of 100 cats selected from a database of a single practice, meniscal mineralization was identified in 37% of the stifles radiographed. Although the cats in the clinical study did not have the presence of meniscal mineralization confirmed by imaging of the menisci, or by histopathology, when the same features were observed in the cadaver study, meniscal calcification was found in every instance. Additionally, we found it relatively easy to find cats with meniscal mineralization for the cadaveric study although we do not know the prevalence of meniscal mineralization in this population of cats. Walker et al[16] described meniscal mineralization to be radiographically evident in 8 of 12 African lions and 6 of 7 Bengal and Bengal-cross tigers (all except 1 were $>$ 1 year of age), but their study did not establish the

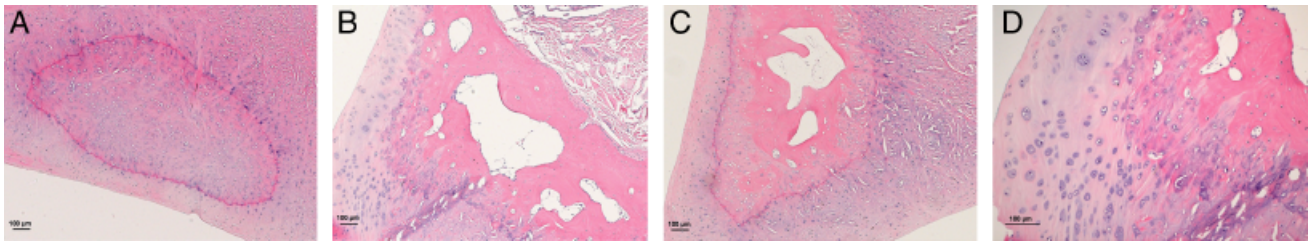


Figure 3 Histology of meniscal mineralization and ossification. Meniscal mineralization appeared as areas of chondro-osseous metaplasia (A) or as organized structures with cancellous bone and bone marrow, surrounded by metaplasia of the fibrocartilage (B, C, and D). Hematoxylin and eosin stain (A, B, C $\times$5; D $\times$10).

prevalence of meniscal mineralization in these species. Meniscal mineralization has been reported in dogs[13,14] but the prevalence in the canine population is unknown. In humans, regional mineralization of the knee meniscus is a rare finding with an incidence of 0.15% according to a study where 1287 patients were evaluated with magnetic resonance imaging.[10] Approximately 50 cases of human meniscal mineralization have been reported, mainly in case reports.[6–12,19]

Compared with cats with no radiographically visible pathology, cats with suspected meniscal mineralization and no other radiographic lesions were significantly older, weighed less, and had a lower BCS. If meniscal mineralization is associated with DJD, then these associations likely represent an association between age and DJD. It is known that cats tend to lose weight and BCS as they get older.[20–22]

Quantifying meniscal mineralization and investigating the relationship to DJD has not been reported in cats, dogs, or humans. Kapadia et al[15] reported the volume of meniscal mineralization in the menisci of 2 age groups (6 and 24 month old) of guinea-pigs using micro-computed tomography. In both age groups, the ossified region of the medial meniscus was significantly larger than the lateral meniscus. The volume of the medial meniscal mineralization increased significantly between 6 and 24 months of age, and the medial compartment of the stifle had more new bone formation, which was also associated with increasing age. It was suggested that the bone remodeling and cartilage degeneration evident in the medial compartment of the stifle joint could be a consequence of the presence of ossification of the medial meniscus which might have altered the joint biomechanics and, in part, initiated medial compartment joint degeneration. The authors suggested that meniscal mineralization in guinea-pigs, being a model of osteoarthritis (OA), could offer insights into the role of the meniscus in the development of OA in humans as well. The present study, showed a clear relationship between meniscal mineralization and cartilage damage on the medial femoral condyle and medial tibial plateau. However, it is not known if the meniscal mineralization is a cause, or result of the cartilage damage. The fact that there was more cartilage damage on the medial tibial plateau compared with the lateral tibial plateau in the normal stifles might suggest that meniscal mineralization is a response to degenerative changes.

As with Kapadia et al,[15] our results suggest that meniscal mineralization may be associated with medial compartment joint disease of the stifle joint in cats. In people, medial compartment DJD of the knee has been associated with high adduction moment at the knee during ambulation.[23–27] It may be that gait patterns, alteration of gait patterns, or pelvic limb conformation in some cats may predispose to meniscal mineralization, and this may in turn hasten the progression of DJD. This of course is speculative, but further investigation of the condition in cats may help in preventing the disease in this species, and may reveal a naturally occurring model of medial compartment pathology that could be used to study the disease in people.

The high correlation ($r^2 = 0.8$; $P < .0001$) between the percent of the area of the menisci taken up by the meniscal mineralization and subjective total DJD score should be interpreted cautiously since meniscal mineralization was

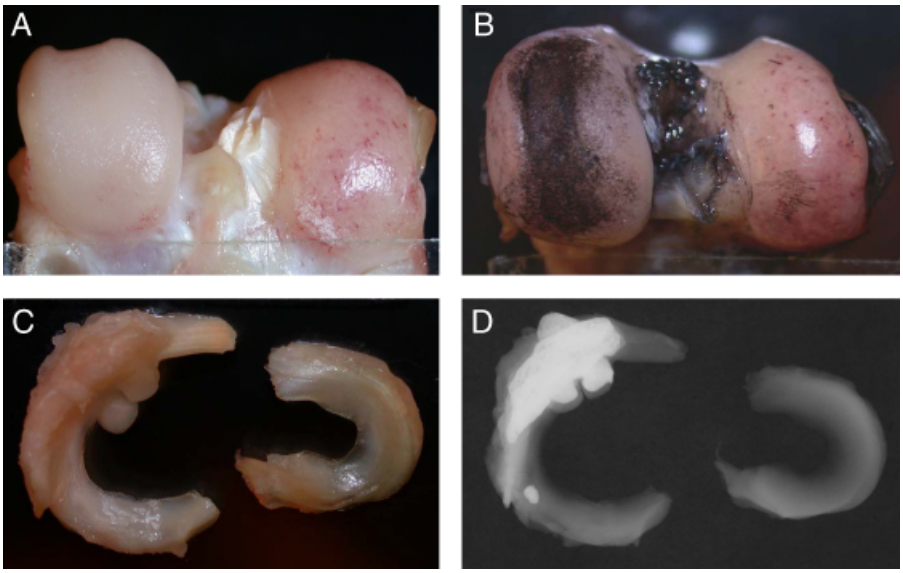


Figure 4 Articular surface of the distal femur of a cadaver specimen showing a distinct groove in the medial femoral condyle (left) (A). Note the retention of India ink by the medial condyle because of fibrillation and erosion of the articular cartilage (B). Appearance of the lateral (right) and medial (left) menisci of the same cadaver specimen (C). Note the normal size of the lateral menisci, compared with the irregularly shaped and enlarged medial menisci. High detail (Faxitron) radiographs showed mineralization of the medial menisci (D) (43% of the total area of the medial meniscus is taken up by the mineralization).

one of the radiographic features considered indicative of DJD and its detection on radiographs contributed directly to increase the total DJD score. The case with the largest meniscal mineralization we describe (55% of the total area of the meniscus) had a distinct groove in the medial femoral condyle and it appeared the mineralization of the medial meniscus had been articulating with the femur (Fig 4). A previous study also reported the presence of a groove in the medial femoral condyle that articulated with an ossicle of the medial meniscus in the stifle joint of a tiger (*Pantera tigris*).[2] In that report, the authors suggested that the ossicles within the medial meniscus were a normal adaptive anatomic feature that helped distribution of load through the meniscus thereby reducing wear and fatigue of the articular surfaces of the femur and tibia. In contrast to this, we consider the changes in the medial femoral condyle to be degenerative, likely in response, at least in part, to the presence of the meniscal mineralization.

The cause of meniscal ossification is debated. Our histologic findings seem to suggest that menisci undergo a process of ossification, starting with a chondro-osseous transformation of the fibrocartilage with mineral deposition, ultimately organizing into cancellous bone and bone marrow structure. That the ossified areas continue to grow by conversion of fibrocartilage to bone is suggested by the presence of chondro-osseous metaplasia of the fibrocartilage observed in the periphery of the ossified area. The bilateral symmetrical appearance of the meniscal mineralizations could support a nondegenerative origin, however, repetitive microtrauma because of bilateral gait abnormalities, or pelvic limb conformation in some cats could trigger the degenerative transformation at specific areas of the menisci bilaterally. In people, chondrocalcinosis of the meniscus has been associated with several distinct metabolic disorders including hemochromatosis, hyperparathyroidism, and hypothyroidism.[28] The association between metabolic disorders and mineralization of menisci in cats is unknown.

The clinical significance of the presence of meniscal mineralization in domestic cat menisci is unknown. Indeed, our study showed no difference in pain scores between radiographically normal stifles and those with just meniscal mineralization. However, despite all the assessments being performed by a single individual, musculoskeletal pain is difficult to assess in cats. Further work might look at such groups of cats and make the evaluations before and after the administration of a known analgesic.

Using high detail (Faxitron) radiographs as a gold standard for detection of meniscal mineralization, digital radiographs and analog high detail film/screen radiographs were 100% specific and had a high sensitivity for detection of meniscal mineralization (91% and 88%, respectively). Both radiographic techniques are considered acceptable for detection of meniscal mineralization in cats, although some of the smaller areas of mineralization may be missed with both techniques. Given the superior dynamic range afforded by digital imaging, it is not surprising that the digitally acquired images had higher sensitivity.

One criticism of our study is the use of digital images to make measures of cartilage damage. Pilot work using X-ray film and thin plastic or flexible film (parafilm: Pechiney Plastic Packaging Company, Chicago, IL) indicated that the results from using flexible film had a higher coefficient of variation, the lesions in the cartilage were difficult to see through the parafilm, it was very difficult to delineate the lesions with a marker and the flexible film was impossible to place around some surfaces. Measures taken from digital photographs of the articular surface itself, despite being two-dimensional were considered to be more accurate and feasible to be performed for all the surfaces. Additionally, our study was a comparative study of the stifles with and without meniscal mineralization.

Little is known about the origin of meniscal mineralizations in the feline menisci as well as in other species, and the clinical significance of radiographically detected meniscal mineralization is uncertain. However, the presence of meniscal mineralizations is a common condition in domestic cats and seems to indicate medial compartment joint disease. Further work to characterize this phenomenon and its role in the development of DJD in cats is required. A better understanding of this phenomenon in cats could help to understand this process in people and other animals.

REFERENCES

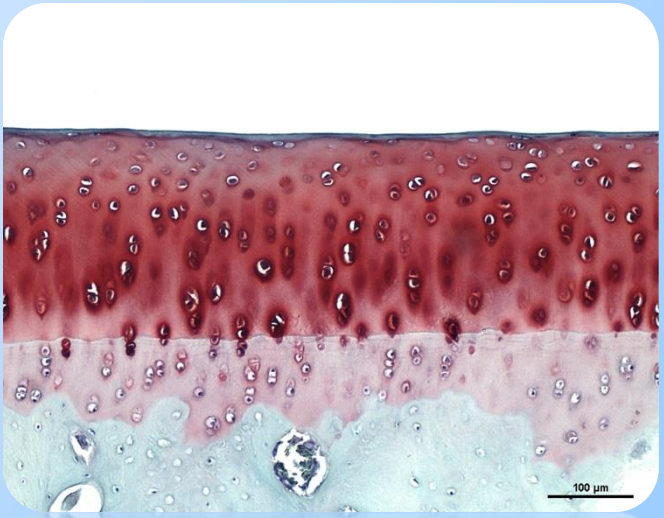
1. Whiting PG, Pool RR: Intrameniscal calcification and ossification in the stifle joints of three domestic cats. *J Am Anim Hosp Assoc* 1985;21:579–584
2. Ganey TM, Ogden JA, Abou-Madi N, et al: Meniscal ossification. II the normal pattern in the tiger knee. *Skeletal Radiol* 1994;23:173–179
3. Kirberger RM, Groenewald HB, Wagner WM: A radiological study of the sesamoid bones and *os meniscus* of the cheetah (*Acinonyx jubatus*). *Vet Comp Orthop Traumatol* 2000;13:172–177
4. Pedersen HE: The ossicles of the semilunar cartilages of rodents. *Anat Rec* 1949;105:1–7
5. Noble J, Hamblen DL: The pathology of the degenerate meniscus lesion. *J Bone Jt Surg* 1975;2:180–186
6. Rosen IE: Unusual intrameniscal lunulae. *J Bone Jt Surg* 1958;4:925–928
7. Liu SH, Osti L, Raskin A, et al: Meniscal ossicles: two case reports and a review of the literature. *Arthroscopy* 1994;10:296–298
8. Yoo JH, Yang BK, Son BK: Meniscal ossicle: a case report. *The Knee* 2007;14:493–496
9. Schaefer WD, Martin DF, Pope TL, et al: Meniscal ossicle. *J Southern Orthop Assoc* 1996;5:126–129
10. Schnarkowski P, Tirman FJ, Fuchigami KD, et al: Meniscal ossicle: radiographic and MR imaging findings. *Radiology* 1995;196:47–50
11. Kato Y, Oshida M, Saito A, et al: Meniscal ossicles. *J Orthop Sci* 2007;12:375–380

12. Ogden JL, Ganey TM, Arrington JA, et al: Meniscal ossification. I Human. *Skeletal Radiol* 1994;23:167–172
13. Reinke J, Mughannam A: Meniscal calcification and ossification in six cats and two dogs. *J Am Anim Hosp Assoc* 1994;30:145–152
14. Weber NA: Apparent primary ossification of the menisci in a dog. *J Am Vet Med Assoc* 1998;212:1892–1894
15. Kapadia RD, Badger AM, Levin JM, et al: Meniscal ossification in spontaneous osteoarthritis in the guinea-pig. *Osteoarthritis Cartilage* 2000;8:374–377
16. Walker M, Phalan D, Jensen J, et al: Meniscal ossicles in large non-domestic cats. *Vet Radiol Ultrasound* 2002;43:249–254
17. Meachim G: Light microscopy of Indian ink preparations of fibrillated cartilage. *Ann Rheum Dis* 1972;31:457–464
18. Yoshioka M, Courtts RD, Amiel D, et al: Characterization of a model of osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage* 1996;4:87–98
19. Le Minor JM, Kempf JF: Ossicule intrameniscal du genou (lunula): a propos d'un cas. Revue de la literature. *Rev de Chir Orthop* 1989;75:501–505
20. Lund EM, Armstrong PJ, Kirk CA, et al: Prevalence and risk factors for obesity in adult cats from private US veterinary practices. *Intern J Appl Res Vet Med* 2005;3:88–96
21. Laflamme DP: Nutrition for aging cats and dogs and the importance of body condition. *Vet Clin Small Anim Pract* 2005;35:713–742
22. Kronfeld DS, Donoghue S, Glickman T: Body condition of Cats. *J Nutrition* 1994;124:2683–2684
23. Guo M, Axe MJ, Manal K: The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. *Gait Posture* 2007;26:436–441
24. Hunt MA, Birmingham TB, Bryant D, et al: Lateral trunk lean explains variation in dynamic knee joint load in patients with medial compartment knee osteoarthritis. *Osteoarthritis Cartilage* 2008;16: 591–599
25. Hurwitz DE, Sumner DR, Adriacchi TP, et al: Dynamic knee loads during gait predict proximal tibial bone distribution. *J Biomech* 1998;31:423–430
26. Mundermann A, Asay JL, Mundermann L, et al: Implications of increased mediolateral trunk sway for ambulatory mechanics. *J Biomech* 2008;41:165–170
27. Zhao D, Banks SA, Mitchell KH, et al: Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *J Orthop Res* 2007;25:789–797
28. Hough AJ, Webber RJ: Pathology of the meniscus. *Clin Orthop Rel Res* 1990;252:32–40

PUBLICATION 4

Pathology of articular cartilage and synovial membrane from elbow joints with and without degenerative joint disease in domestic cats. M Freire, D Meuten, BDX Lascelles. *Veterinary Pathology*. 2014 Jan 29. [Epub ahead of print].

http://www.ncbi.nlm.nih.gov/pubmed/24476939



Article

Veterinary Pathology
1-11

DOI: 10.1177/0300985813516648
vet.sagepub.com

Pathology of Articular Cartilage and Synovial Membrane From Elbow Joints With and Without Degenerative Joint Disease in Domestic Cats

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Abstract

The elbow joint is one of the feline appendicular joints most commonly and severely affected by degenerative joint disease. The macroscopic and histopathological lesions of the elbow joints of 30 adult cats were evaluated immediately after euthanasia. Macroscopic evidence of degenerative joint disease was found in 22 of 30 cats (39 elbow joints) (73.33% cats; 65% elbow joints), and macroscopic cartilage erosion ranged from mild fibrillation to complete ulceration of the hyaline cartilage with exposure of the subchondral bone. Distribution of the lesions in the cartilage indicated the presence of medial compartment joint disease (most severe lesions located in the medial coronoid process of the ulna and medial humeral epicondyle). Synovitis scores were mild overall and correlated only weakly with macroscopic cartilage damage. Intra-articular osteochondral fragments either free or attached to the synovium were found in 10 joints. Macroscopic or histologic evidence of a fragmented coronoid process was not found even in those cases with intra-articular osteochondral fragments. Lesions observed in these animals are most consistent with synovial osteochondromatosis secondary to degenerative joint disease. The pathogenesis for the medial compartmentalization of these lesions has not been established, but a fragmented medial coronoid process or osteochondritis dissecans does not appear to play a role.

Keywords

degenerative joint disease, elbow joint, feline, histopathology, medial compartment joint disease, synovial osteochondromatosis

Appendicular degenerative joint disease (DJD) is a condition commonly present in domestic cats. Prevalence of radiographic signs of appendicular DJD in this species varies with age and has been reported to range from 16.5% to 91%.[5,12,15,19,29] Joints reported to be most commonly affected in prospective studies are hip and stifle[19] or shoulder and elbow.[29] Radiographic evidence of DJD in the elbow joint in cats has a prevalence of approximately 41%, and bilateral disease has been reported in 28% of cases.[19]

The predominant cause of DJD in the cat has not been identified,[18] and it is suggested that most cases of feline DJD are primary or idiopathic.[4,5,12] The elbow joint is commonly affected by DJD in dogs as well,[20] but unlike cats, most canine patients with elbow joint DJD have known underlying predisposing factors such as a fragmented medial coronoid process (FMCP) or osteochondritis dissecans (OCD). To date, these forms of elbow dysplasia have not been proven to be present in cats. One report suggested the occurrence of elbow dysplasia (FMCP) as a cause of elbow disease in a feline patient after removal of several osteochondral fragments from both elbow joints.[31] As part of a separate study, we have observed similar fragments in cats with elbow DJD, in which evidence of macroscopic cartilage damage is present but with apparently intact coronoid processes of the ulna on macroscopic examination.[11] The presence of free ossified fragments has been identified in shoulder, stifle, and elbow joints in cats and considered either osteophytes that have not been completely incorporated within the epiphysis or "osteochondromas" resulting from hyperplasia of the synovial membrane and synovial chondrometaplasia.[2,32] In neither of these studies was a thorough histopathological

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evaluation of the free osteochondral fragments, medial coronoid process, or synovial membrane reported. Histological changes of the humeral condyle in cats with and without DJD have recently been published and suggested concentration of the lesions in the medial part of the humeral condyle,[28] but this work did not evaluate other articular surfaces or the synovial membrane, and it was not designed to look for possible causes of feline elbow DJD.

Even though the prevalence of radiographic signs of DJD in the elbow joint in cats is high and FMCP has been suggested to be present in this species, the etiology of feline elbow DJD is unknown, and the presence of feline elbow dysplasia has not been confirmed. The objective of this study is to report the histological characteristics of the articular surfaces, synovial membranes, and intra-articular osteochondral fragments in elbow joints from cats with and without DJD and compare the findings with those reported to be present in dogs with FMCP. We hypothesized that elbow joints with macroscopic evidence of DJD and the presence of intra-articular osteochondral fragments had histological evidence of a fragmented coronoid process (similar to dogs) and that the degree of macroscopic and histological damage of the articular surfaces correlated with the severity of synovial inflammation and hyperplasia.

Materials and Methods

This study was a prospective study using autopsy material.

Animals

Thirty adult cats, scheduled for euthanasia at a local animal shelter, were included. These animals were part of a previous study performed by the same laboratory.[11] Selection of these animals was such that will increase the likelihood of finding animals with different degrees of osteoarthritis (eg, selecting for older animals to increase the chance of finding joints with DJD). Animals were euthanized with an overdose of barbiturates for reasons unrelated to this study (population control). Age and sex of the cats were recorded. Clinical history of these animals prior to euthanasia was not known.

Macroscopic Examination

Immediately after euthanasia, both elbow joints of each cat were opened and the joints were visually inspected for the presence of macroscopic lesions as described previously.[11] The articular cartilage of the humerus, radius, and ulna of each joint was evaluated grossly for fibrillation and/or erosion of the cartilage surface using India ink[23] as previously reported.[11] Briefly, after gross observations were recorded, the cartilage surfaces were painted with India ink twice, rinsing the cartilage with water 3 minutes after the ink was applied. The severity of surface damage of the articular cartilage was scored based on ink retention and graded according to the scale described in a previous study:[33] grade 1—intact surface: surface appears normal and does not retain any ink; grade 2—minimal fibrillation: site appears normal before staining but retains India ink as elongated specks or light gray patches; grade 3—overt fibrillation: the cartilage is velvety in appearance and retains ink as intense black patches; and grade 4—ulceration: loss of cartilage exposing the underlying bone. Only severity of cartilage damage was graded, independently of the extent of the lesion.

Early during the dissection, the medial coronoid process was also grossly evaluated for the presence of cartilage fissures or intra-articular fragments that could be secondary to medial coronoid fragmentation.

Histopathology of Elbow Joints

Following macroscopic examination, a section containing the articular surfaces of the proximal ulna and radius and distal humerus, as well as a sample of the joint capsule/synovium, was immediately placed in 10% neutral buffered formalin for at least 48 hours. Decalcification of the bone specimens was achieved using 10% formic acid solution for a variable time length (7–14 days) depending on the size of the samples. After decalcification, sections perpendicular to the articular surfaces of each bone were cut making sure the area with the most severe macroscopic cartilage fibrillation was included. These sections were performed so that they included the coronoid and anconeal processes of the ulna in all cases following a parasagittal plane. Sections of the humerus and radius were performed in the frontal plane. Two serial sections of the bone specimens were mounted onto glass slides and stained with hematoxylin and eosin (HE) and Safranin-O (SO). Sections of joint capsule/synovium were stained with HE. Osteochondral fragments found within the joint or attached to the joint capsule were collected, processed, and stained in the same manner as the bone specimens.

The bone, joint capsule, and osteochondral fragments were evaluated microscopically (Olympus microscope BX41TF [Olympus America, Center Valley, PA]; Nikon microscope camera DS 2Mv [Nikon, Tokyo, Japan]). A descriptive approach was used to evaluate the histological changes present in the articular cartilage and subchondral bone, using combination of the Mankin and OARSI (Osteoarthritis Research Society International) histological and histochemical scoring systems to create a unique scoring system relevant to this study (Suppl. Table S1).[21,26] This enabled semi-quantitative evaluation of structural changes in all layers of the uncalcified hyaline cartilage, calcified cartilage zone, tidemark integrity, and the intensity of SO staining as well as changes identified in the subchondral bone. The sections were evaluated at different magnifications for the individual parts of the scoring system. The degree of synovitis was evaluated and graded using the grading system previously described by Krenn et al[17] (Suppl. Table S2). Changes observed in 3 histologic structures (synovial lining cell layer, stroma cell density, and inflammatory infiltrate) were assigned a numerical score: none (0), slight (1), moderate (2), and strong (3). These individual scores were summed to determine a final total score, and the final scores for each sample were interpreted as follows: 0 to 1, no synovitis; 2 to 4, low-grade synovitis; and 5 to 9, high-grade synovitis. Evaluation was performed

Table 1. Details of the Severity Grades of Macroscopic Cartilage Damage of the Humerus, Radius, and Ulna Articular Surfaces.

	Macroscopic Grading System—India Ink Retention Score				
	Grade 1	Grade 2	Grade 3	Grade 4	Score, Mean (SD)
Humerus ($n = 60$)	21	21	9	9	2.1 (1.05)
Radius ($n = 60$)	25	33	2	0	1.6 (0.5)
Ulna ($n = 60$)	19	24	8	9	2.1 (1.02)
Total ($N = 180$ bones)	65	78	19	18	

Grade 1, no lesions; grade 2, mild fibrillation; grade 3, moderate fibrillation; grade 4, cartilage ulceration.

at the area of the specimen with the most marked histopathological alterations.

Statistical Analysis

The mean $\pm$ standard deviation (SD) macroscopic and microscopic cartilage damage scores of the ulna, humerus, and radius were compared using the Wilcoxon signed-rank test. Bonferroni correction for multiple comparisons was used, and results were considered significantly different when $P < .016$. Spearman's rank correlation coefficient was used to assess correlation between synovitis scores of each joint and the worse macroscopic and microscopic cartilage damage scores (the highest score of the 3 bones of each joint). Values of $P < .05$ were considered significant.

Results

A total of 30 animals were included in the study. There were 19 females and 11 males. Age was known in 18 animals and ranged from 7 to 19 years. Because of unknown previous history, age was speculated in 12 animals; 9 were considered young adults (age range approximately between 2 and 7 years), and in 3, age was suspected to be at least between 10 and 13 years.

Macroscopic Findings

Twenty-two of the 30 cats (73.3% of cats; 39 elbow joints; 115 of 180 bones; 64% of all articular surfaces) had macroscopic lesions of the articular cartilage that ranged from mild fibrillation to complete ulceration of the cartilage with exposure of the subchondral bone. Sixty-five articular surfaces (36%) were grossly normal, and there was no retention of India ink (grade 1); 78 (43%) had mild macroscopic cartilage fibrillation (grade 2); 19 (11%) had severe macroscopic cartilage fibrillation (grade 3); and 18 (10%) had complete ulceration of the articular cartilage with exposure of the subchondral bone (grade 4) (Table 1; Fig. 1).

Macroscopic cartilage lesions were bilateral when present, and the degree of damage to the articular surfaces was similar in both elbow joints. Macroscopic lesions of the articular cartilage with the most severe degree of cartilage erosion were located in the medial compartment of the joints (articular surface of the medial coronoid process and medial aspect of the humeral condyle). All animals that did not have macroscopic lesions were young adults (estimated between 2 and 7 years of age), and the most severe lesions with ulceration of the cartilage were found only in animals older than 10 years.

Microscopic Findings

The articular surface of 180 bones (radius, ulna, and humerus of each elbow joint) was evaluated grossly, with 176 bones evaluated histologically (4 specimens were not processed appropriately and slides were not considered of sufficient quality for evaluation). These 176 samples represent 1 section from each of the 3 bones comprising the elbow joint, taken bilaterally from 30 cats.

Of the 64 grossly normal articular surfaces that were evaluated histologically, 40 were histologically normal and abnormalities were detected in 24 specimens. Of the 112 grossly abnormal articular surfaces evaluated histologically, 10 were histologically normal and 102 were histologically abnormal (Table 2). Histological abnormalities are described below.

Histological Characteristics of Macroscopically Normal Samples

Sixty-four samples with no India ink retention by the cartilage were evaluated histologically; of those, 40 samples were also considered microscopically normal. These samples were characterized by the absence of cartilage fibrillation, normal density and number of chondrocytes organized in columns, normal intensity of SO staining, a single tidemark not crossed by blood vessels, and absence of changes in the subchondral bone, such as no increase in woven bone or islands of cartilage or fibrosis in the bone marrow spaces (Suppl. Figure S1). Microscopic lesions were observed in 24 samples without any evidence of macroscopic fibrillation of the cartilage (no India ink retention by the cartilage surface). These lesions were characterized by moderate to severely decreased SO staining, decreased number and size of chondrocytes, and occasionally deep fissures separating the hyaline cartilage from the deeper calcified cartilage (at the level of the tidemark; 4 specimens) (Fig. 4). No superficial fibrillation of the hyaline cartilage was present in these cases. These lesions were always observed as focal, particularly in the ulna, located in the articular cartilage covering the coronoid process. Fissures or microfractures of the subchondral bone at this level that could indicate deeper lesions or diseases involving the subchondral bone were not observed.

Figure 1. Humeral condyles; cat. Macroscopic cartilage fibrillation grades 1 to 4 using the India ink retention grading system. (a) Cartilage fibrillation grade 1, no ink retention. (b) Cartilage fibrillation grade 2 or mild fibrillation in a specimen in which cartilage fibrillation was difficult to appreciate before ink application. (c) Cartilage fibrillation grade 3 or moderate fibrillation. In this joint, degenerative joint disease was grossly evident before ink application. (d) Cartilage fibrillation grade 4 or cartilage ulceration with exposure of the subchondral bone, which does not retain ink. **Figure 2.** Elbow joint; cat No. 24. Intra-articular osteochondral fragment. A free intra-articular osteochondral fragment is present in the cranial aspect of the elbow joint. The fragment is next to the medial coronoid process of the ulna and medial epicondyle of the humerus. **Figure 3.** Intra-articular osteochondral fragments; cat No. 24. Three intra-articular osteochondral fragments found in the same elbow displayed in Fig. 2. The 2 larger fragments were in the cranial aspect of the joint, one free and the other attached to the joint capsule. Size of intra-articular fragments ranged from 3 to 6 mm. This animal had intra-articular osteochondral fragments in both elbows.

Table 2. Distribution of Macroscopic and Histological Normal and Abnormal Articular Surfaces by Bones.

		Histologically	
Macroscopically		Normal	Abnormal
Normal ($n = 64$)	Humerus	15	5
	Radius	17	8
	Ulna	8	11
Abnormal ($n = 112$)	Humerus	6	33
	Radius	4	31
	Ulna	0	38
Total ($N = 176$)		50	126

Adjacent to the focal lesions, which were approximately 400 to 500 μm in length, the articular cartilage was normal.

Histological Characteristics of Macroscopically Abnormal Samples

Macroscopic fibrillation of the articular surfaces was accompanied by microscopic lesions in 102 of the 112 macroscopically abnormal samples evaluated. Ten specimens with macroscopic fibrillation of the cartilage were considered normal histologically. Histological lesions were characterized by different degrees of fibrillation of the hyaline cartilage, decreased intensity of SO staining, decreased number and size of chondrocytes as well as disorganization of the chondrocyte columns, and changes in the subchondral bone.

In cases with mild or moderate degrees of macroscopic cartilage damage (India ink retention grades 2 and 3), the histological lesions were also relatively mild or moderate and consisted of cartilage surface discontinuity with vertical fissures extending into the superficial, mid, or deep zones; occasionally, fissures extending into the calcified cartilage zone or the subchondral bone were also observed. Cell death was identified adjacent to the fissures, but chondrocyte proliferation was not appreciated in those areas. SO staining in areas of cartilage fibrillation was of variably decreased intensity, from slightly decreased to no staining at all (Figs. 5, 6). Lesions observed in the subchondral bone immediately below the articular cartilage were classified as mild and were characterized by fibrosis in the bone marrow spaces with occasional foci of cartilage islands. The amount and distribution of woven bone in the subchondral bone was considered abnormal in 3 cases with macroscopic cartilage damage classified as grade 3.

Cases with the most severe degree of macroscopic cartilage damage (India ink retention grade 4) showed complete ulceration, with hyaline cartilage matrix loss exposing the calcified cartilage zone or the subchondral bone to the intra-articular space (Fig. 7). Cell death was identified adjacent to the fissures and hypertrophic chondrocytes were occasionally seen adjacent to areas of severe cartilage fibrillation, but chondrocyte proliferation was not identified in those areas (Fig. 8). SO staining adjacent to the areas of severe cartilage fibrillation was severely decreased in intensity or absent in all cases. Changes in the subchondral bone (fibrosis/cartilage islands and/or woven bone) were present in all cases with grade 4 macroscopic cartilage fibrillation. Fibrosis and cartilage islands in the subchondral bone ranged from mild to severe. These areas appeared as discrete foci of hypertrophic chondrocytes embedded in the chondroid matrix (“cartilage islands”) and/or fibrovascular granulation tissue filling bone marrow spaces in close proximity to the exposed subchondral bone surface (Fig. 9). Replacement of mature lamellar bone by woven bone was detected by polarizing light in 8 of 18 cases with severe macroscopic cartilage damage, and in these cases, the articular surface was completely ulcerated and the subchondral bone exposed. Woven bone was always surrounding the areas of cartilage islands and bone marrow spaces that were filled with fibrosis.

Changes in the density of the subchondral bone were not appreciated. The tidemark was intact, single, and not crossed by blood vessels in any case, including those with severe damage of the articular cartilage.

Medial Coronoid Process

Visual inspection of the medial coronoid process did not reveal the presence of fissures in the cartilage, in situ fractured coronoid fragments, or free fractured fragments within the joint. In those joints in which intra-articular osteochondral fragments were present, the coronoid process was macroscopically intact. Microscopically, fissuring of the subchondral bone of the medial coronoid process was not identified in any cases, neither in cases with intact overlying articular cartilage nor in cases with severe cartilage damage. Subjective evaluation of cartilage thickness, osteocyte density of the subchondral bone, and bone porosity in the subchondral bone of the coronoid process was normal.

Relationship of Macroscopic and Microscopic Lesions Between Different Bones Within a Joint

Macroscopic cartilage damage scores (mean $\pm$ SD) using the India ink grading system were significantly higher for the ulna (2.1 ± 1.02; $P = .0001$) and the humerus (2.1 ± 1.05; $P < .0002$) compared with the radius (1.6 ± 0.5). No differences were found when the ulna and humerus were compared ($P = .7$) (Table 1). Macroscopic cartilage lesions were bilateral, and the degree of damage of the articular surfaces was similar in both elbow joints. The location of the lesions with the most severe cartilage fibrillation indicated the presence of disease in the medial compartment of the elbow joint with the articular surface of the medial coronoid process and the medial epicondyle of the humerus having the most severe degree of cartilage fibrillation.

Microscopic cartilage damage scores (mean $\pm$ SD) were significantly higher for the ulna (5.54 ± 4.3) compared with the radius (2.5 ± 2.6; $P < .0001$) and the humerus (3.8 ± 3.9; $P < .0001$). Microscopic cartilage damage scores were also significantly higher for the humerus compared with the radius ($P = .007$).

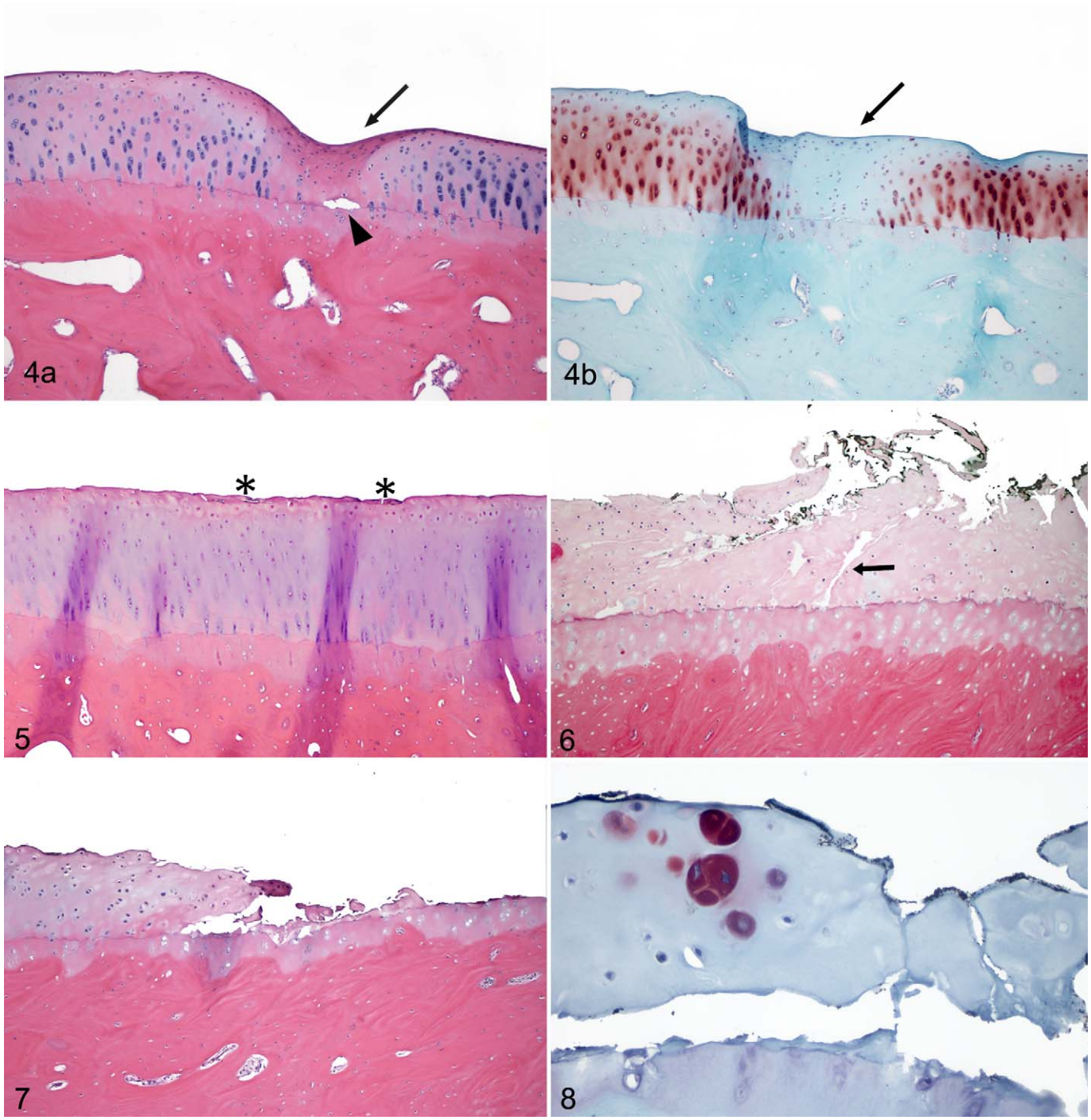

Figure 4. Ulna; cat No. 21. Early histological lesions in articular cartilage. (a) Superficial cartilage fibrillation is not present. A focal area of disorganization and decreased number of chondrocytes is present (arrow). A fissure is separating the hyaline cartilage from the calcified cartilage zone, at the level of the tidemark (arrowhead). Macroscopic appearance of this articular cartilage was normal. Hematoxylin and eosin (HE). (b) The affected area has loss of Safranin-O (SO) staining (arrow). **Figure 5.** Humerus; cat No. 18. Mild cartilage fibrillation. Superficial fibrillation of the articular cartilage with fissures that extend into the superficial/mid-zone of the hyaline cartilage (asterisks). Mild disorganization and decreased number of chondrocytes in the affected area are present. Area of cartilage and subchondral bone with increased stain intensity is a folding artifact. HE. **Figure 6.** Ulna; cat No. 23. Moderate cartilage fibrillation. Multiple vertical fissures extend into the deep zone of the hyaline cartilage (arrow), the number of chondrocytes is decreased, and cell death would be appreciated at higher magnification adjacent to the fissures. Black staining in the fissures is India ink retention. Cell proliferation is not present. HE. **Figure 7.** Ulna; cat No. 24. Severe cartilage fibrillation with ulceration. Cartilage fibrillation with ulceration and exposure of the calcified cartilage zone is present. In the hyaline cartilage adjacent to the ulcerated region, decreased size and number of chondrocytes is evident. HE. **Figure 8.** Ulna; cat No. 22. Occasionally, hypertrophic chondrocytes were appreciated adjacent to areas of severe cartilage fibrillation. Cell proliferation with clusters of normal-sized chondrocytes was not seen in any case. SO.

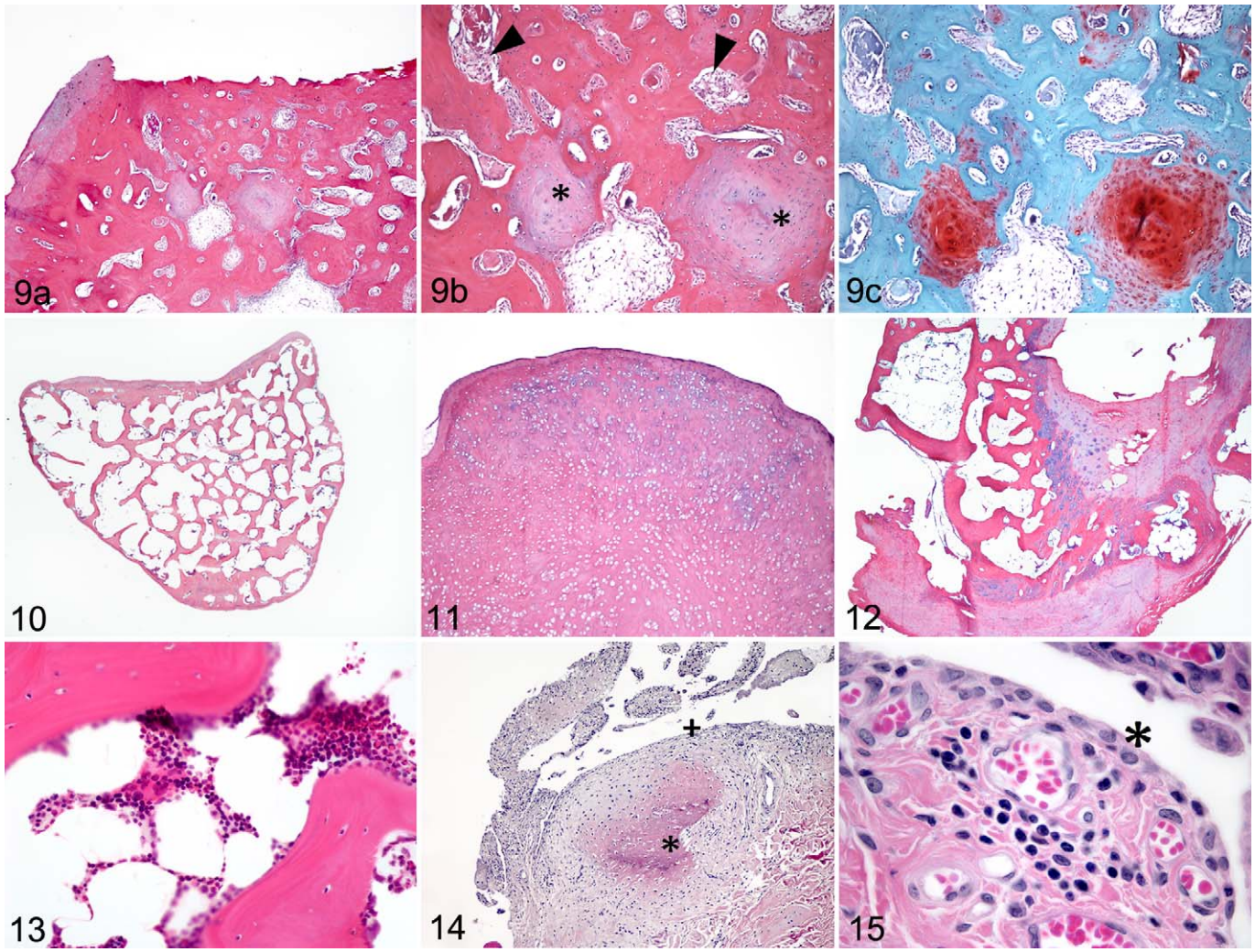

Figure 9. Ulna; cat No. 24. Cartilage ulceration and subchondral bone lesions. (a) Articular surface of the ulna is ulcerated with exposure and erosion of the subchondral bone. The subchondral bone underneath the ulcerated articular surface has fibrosis in the bone marrow spaces and cartilage islands. New woven bone was located surrounding the cartilage islands and bone marrow spaces filled with fibrosis. Hematoxylin and eosin (HE). (b) Higher magnification view of the subchondral bone with cartilage islands (asterisks) and fibrovascular granulation tissue filling the bone marrow spaces (arrowheads). HE. (c) Foci of cartilage in the subchondral bone are highlighted by uptake of Safranin-O (SO) stain. **Figure 10.** Intra-articular osteochondral fragment; cat No. 15. Image shows an intra-articular osteochondral fragment composed exclusively of cancellous bone with well-organized trabeculae and marrow spaces. HE. **Figure 11.** Intra-articular chondral fragment; cat No. 24. Some intra-articular fragments were composed exclusively of fibrocartilage, chondroid matrix, and chondrocytes as the one shown in the image. They were surrounded by a thin layer of dense fibrous tissue similar to the fragment shown in Fig. 10. HE. **Figure 12.** Intra-articular osteochondral fragment; cat No. 15. In most cases, osteochondral fragments were composed of a mixture of trabecular bone with marrow spaces, hyaline cartilage, and areas of fibrous tissue. HE. **Figure 13.** Intra-articular osteochondral fragment; cat No. 28. Two trabeculae of viable bone reside on each side of hematopoietic cells. HE. **Figure 14.** Synovial membrane; cat No. 24. Chondroid metaplasia. Chondroid metaplasia of the synovial stroma was characterized by foci of cartilage (asterisk) in various stages of differentiation that progressed into endochondral ossification. Areas of metaplasia were not associated with inflammatory infiltrates (score 1—few, mostly perivascular infiltrates). Synovial hyperplasia is not a prominent feature of this disease. Synovial lining (+) in this case showed only mild synovial hyperplasia (score 1—lining cells form 2–3 layers). HE. **Figure 15.** Synovial membrane; cat No. 6. Lymphoplasmacytic infiltrates. Synovial lymphoplasmacytic infiltrates, score 1 (as observed in most cases). The lymphoplasmacytic infiltrates are located perivascularly in the synovial stroma, with little to no hyperplasia of the overlying synovium (asterisk). This degree of inflammation in some cases corresponded with severe cartilage fibrillation and ulceration. HE.

Intra-articular Osteochondral Fragments

A total of 16 intra-articular osteochondral fragments were evaluated grossly and histologically. Those fragments were found in 10 joints (affecting 6 different animals). The articular cartilage was ulcerated in at least one of the bones in all of those joints except in 2, in which the macroscopic cartilage damage was scored as 2 (mild cartilage fibrillation). Six joints had single fragments and 4 joints had multiple fragments. These fragments were either attached to the synovial membrane or free as intra-articular bodies. Macroscopically, the osteochondral

fragments where white to pink, flat oval to round, and ranged from 3 to 6 mm (maximum length) (Figs. 2, 3). Microscopically, these fragments contained different amounts of well-organized cancellous bone with marrow spaces that occasionally contained hematopoietic cells. Some fragments also contained hyaline cartilage and fibrocartilage. Different stages of endochondral ossification were present in those areas of mixed tissue types. The outermost layer was commonly a thin layer of dense fibrous tissue. More commonly, a mixture of different tissue types was found, but occasionally fragments were exclusively of either fibrocartilage or organized trabecular bone (Figs. 10–13).

Synovial Membrane Findings

A total of 56 synovial membrane tissue samples were evaluated histologically (from 56 different elbow joints). Four samples from elbow joints of 4 different animals were not considered of appropriate quantity or quality for histological evaluation and were not graded. Overall, there was only mild inflammation in the synovium, very little synovial hyperplasia, and only weak correlation of synovial lesions with severity of macroscopic and microscopic cartilage lesions. Final synovitis scores of all samples evaluated ranged from 0 to 5 (maximum possible score = 9).

Synovial membrane samples considered normal (final score 0–1; $n = 32$) were characterized by normal synovial lining cell layer thickness, normal cellularity of the synovial stroma, and no inflammatory infiltrate present (Suppl. Table S2). The macroscopic cartilage damage score (the highest score of the 3 bones) of those joints with normal synovial membrane samples ranged from 1 to 4 (normal to severe cartilage fibrillation). Synovial membrane samples with the highest synovitis scores (4–5; $n = 9$) were characterized by moderate enlargement of the synovial lining layer (score 2), mild increase in density of resident cells (score 1), and mild inflammatory infiltrate (score 1). Inflammatory infiltrates consisted of lymphoplasmacytic micronodules located perivascularly in the synovial stroma (Fig. 15). The macroscopic cartilage damage score (the highest score of the 3 bones) of those joints with the highest microscopic scores for the synovial membrane samples ranged from 2 to 4 (mild to severe cartilage fibrillation).

The synovial lining was never ulcerated, and multinucleated cells were never seen in the synovial lining cell layer or in the synovial stroma, even in cases in which the subchondral bone was denuded of articular cartilage. None of the samples had inflammatory infiltrates graded as severe (score 3), and only 2 synovial membrane samples (joints from the same animal) had an inflammatory infiltrate graded as moderate (score 2).

Microscopic changes different from those evaluated for the synovitis severity score were observed. Chondroid metaplasia of the synovial stroma was identified in 2 cases. These areas appeared as micronodules of metaplasia of the hyperplastic synovium into cartilage, of varying stages of differentiation that seemed to undergo endochondral ossification to form bony nodules in some cases. These areas of metaplasia were not associated with inflammatory infiltrates (Fig. 14).

Synovitis severity scores were significantly but weakly and moderately correlated with the highest macroscopic ($r^2 = 0.3768$; $P = .0042$) and microscopic ($r^2 = 0.4226$; $P = .0012$) cartilage damage scores of the joints, respectively.

Discussion

Results of this study are the first description of the histopathological characteristics of feline elbow joints with and without macroscopic DJD lesions. Lesions were present bilaterally, and the ulna was the bone with the most severe degree of cartilage damage in both macroscopic and microscopic cartilage damage scoring systems. Cartilage lesions ranged from superficial fibrillation of the cartilage to complete ulceration with exposure of the subchondral bone. The most severe macroscopic as well as histological lesions of the articular surfaces were identified within the medial compartment of the elbow joint, specifically in the medial coronoid process of the ulna and the medial epicondyle of the humerus. Medial compartmentalization of the lesions in feline elbow joints has been documented macroscopically elsewhere,[2] and concentration of microscopic lesions in the medial part of the humeral condyle also has been documented.[28] Medial compartment elbow disease is well recognized in dogs as a result of elbow dysplasia (FMCP and OCD of the medial humeral epicondyle).[3,9,24] However, our observations did not reveal any of the features that are reported in dogs with a fragmented coronoid process (microcracks in the subchondral bone, increased porosity, and loss of osteocytes).[6,13] Histomorphometry was not performed in our study, but increased porosity and decreased osteocytes were seen only in the areas of microcracks of the subchondral bone in dogs, and microcracks were not present in our specimens. It is possible that fissures may have been missed during processing of the samples for histopathological evaluation. Nevertheless, since no evidence of FMCP or a histologic reaction to an adjacent microfracture was present in any of the specimens and fissuring or fracture of the coronoid process was not seen during macroscopic evaluation of any joints, we conclude that fragmentation of the coronoid process is not part of the pathogenesis of feline elbow DJD in the cases described in this study. Some of the changes observed in the subchondral bone in the samples evaluated in this study are similar to those described in the subchondral bone of the medial coronoid process from dogs with FMCP disease (cartilage islands and fibrosis of the bone marrow spaces).[13] These lesions are nonspecific responses of bone to a variety of insults and are not unique to FMCP. Unlike lesions in the canine coronoid processes, subchondral bone changes in the feline samples evaluated here were present only when cartilage erosion was so severe that the hyaline cartilage was ulcerated. In the canine study by Goldhammer et al,[13] hyaline cartilage was still present on the articular surface of the medial coronoid process in cases with cartilage islands in the subchondral bone. The cartilage islands within the subchondral bone lesions were likely secondary reactions to the disease that

leads to medial coronoid fragmentation, unlike in our samples in which subchondral bone findings were likely consequence of the degree of cartilage degradation rather than pathology originating in the subchondral bone.

The cause of elbow DJD in cats with this pattern of medial compartmentalization is unknown. One of the theories proposed for the pathogenesis of FMCP in dogs is the presence of abnormal loading forces in the elbow joint resulting from asymmetric growth of the radius and the ulna, which causes increased loads in the coronoid process and subsequent fragmentation. Perhaps the same theory could explain why the lesions are concentrated in the medial compartment of the elbow joints in cats. However, further investigation will be necessary to elucidate why fragmentation of the medial coronoid process does not happen as a result of these theoretical abnormal loadings in feline species. One possibility is that cats do not have underlying lesions of OCD in their coronoid processes, since we did not see evidence of osteochondritis or OCD in any of the samples examined. A less likely possibility is that erosion of the cartilage of the medial coronoid process and medial humeral epicondyle is due to contact with the intra-articular osteochondral fragments, which were commonly located craniomedial in the elbow joint in close proximity to the coronoid process. However, this pattern of medial compartmentalization of the cartilage damage was also observed in joints without intra-articular osteochondral fragments, so this does not fully explain the pattern of cartilage damage observed herein.

Histopathological characteristics of the free intra-articular osteochondral fragments and changes observed in the synovial stroma (chondroid metaplasia and endochondral ossification) seem to indicate that those fragments originate from the synovial membrane and therefore are consistent with synovial osteochondromatosis secondary to DJD. Unlike primary synovial osteochondromatosis, in the secondary form, the intra-articular nodules are less numerous and often mixed with other forms of synovial proliferation and metaplasia, as well as with erosive changes in the articular cartilage that are more marked than is the degree of synovial proliferation,[22,25] which is consistent with our findings. A few cases of synovial chondromatosis in canine species are described in the literature, affecting shoulder, stifle, elbow, and tarsal joints.[1,7,8,10,14,30] Mention of feline synovial chondromatosis in the literature is scarce. In older publications, diagnosis was made based on radiographic findings without gross or histopathological confirmation.[16] In more recent reports, intra-articular mineralizations found in shoulder and elbow joints are referred to as "osteochondromas," but macroscopic and histopathological characteristics are consistent with synovial osteochondromatosis as described in this study.[2] These intra-articular fragments may not be visible radiographically depending on their degree of calcification, and so it is possible that synovial osteochondromatosis with articular cartilage erosion may be present in some joints without radiographic evidence of DJD as has been published previously.[11]

Severe synovial inflammation was not seen in any of the samples evaluated, and overall there was only mild inflammation in the synovium and very little synovial lining hyperplasia even in those elbow joints in which the articular cartilage was ulcerated. This suggests that the elbow lesions in our cases were not primarily inflammatory in origin. The joints with the most severe cartilage fibrillation tended to have the highest synovitis scores, but correlations of the degree of synovitis with macroscopic and microscopic cartilage damage scores were only weak and moderate, respectively. Goldhammer et al[13] reported the degree of synovitis in dogs with different degrees of cartilage fibrillation secondary to FMCP, and similar to our study, the synovitis scores were low, even in cases with ulceration of the articular cartilage. These results are consistent with synovitis scores reported by Krenn et al,[17] in which the mean synovitis score of patients diagnosed with osteoarthritis was only 2 (range, 0–6). It is not surprising, then, that ulceration of the epithelial lining of the synovial membrane or severe inflammatory infiltrate of the synovial stroma was not seen in our samples since these features seem to correspond only with reactive or rheumatoid arthritis. The degree of synovitis present in dogs with synovial osteochondromatosis has not been reported, but clinically these animals have pain on manipulation of the joints. If the degree of synovitis is mild, as we found in the feline samples, the source of pain in these patients may be coming from a source other than the inflamed synovial membrane.

Twenty-four samples considered normal macroscopically were found to be abnormal on histopathologic evaluation. The lesions observed histologically could be considered early changes in the process of cartilage degradation, before any abnormalities are detected on the cartilage surface. Initially, clefts deep in the hyaline cartilage without any superficial fibrillation were suspected to be processing artifacts, as has been suggested in other studies.[13] However, a decrease in the number of chondrocytes and a decrease in SO staining in those areas were also seen, and so the changes were considered real. These results are in agreement with a recent publication in which diffusion parameters (diffusion-weighted spin-echo magnetic resonance imaging sequences) were used to assess disease progression of the articular cartilage, and results suggested that collagen architecture in the deep cartilage is altered early in the process of cartilage damage.[27] These recent findings conflict with the current histopathological grading systems, which are based on the assumption that cartilage damage is initiated at the cartilage surface and propagates deeper into cartilage as osteoarthritis progresses. On the other hand, 10 samples evaluated were graded normal histologically but abnormal macroscopically (Indian ink was retained by the articular surface). In these cases, the area and the degree of ink retention was minimal, and it may represent only mechanical disruption of the articular surface rather than the result of altered collagen architecture and cartilage degradation. In addition, the areas of cartilage fibrillation were so small that it is possible that they were missed during processing.

In addition to subjective comparisons between the lesions present in elbow joints of our cats with lesions reported in other species, we used established scoring systems to grade the changes present in our samples of cartilage, bone, and synovium. After evaluation of articular surfaces that had lesions

of varying severities, it was noted that some of the features used to differentiate severity grades in established grading systems were not present in our samples. The grading system by Mankin et al[21] considers features such as chondrocyte cloning, presence of pannus, or blood vessels crossing the tidemark as indicators of cartilage degradation, and these were not identified in the specimens we evaluated; also, the Mankin system does not evaluate subchondral bone changes. In the same way, the OARSI system[26] establishes grades of cartilage degradation using some features that could not be observed in the samples we evaluated (eg, cartilage edema, chondrocyte clustering), and even though this system included evaluation of changes in the subchondral bone, the changes to be evaluated also differed from our observations. For these reasons and since these systems have not been validated in feline species, we developed a scoring system relevant for this study that considered features observed in the specimens evaluated. The modification of the scoring system proposed here may be a useful reference for the evaluation of cartilage damage in other animal species for which the previously reported systems are not fully applicable as in feline joints.

On the basis of our results, we reject the hypothesis that elbow joints with macroscopic evidence of DJD and the presence of intra-articular osteochondral fragments have histological evidence of a fragmented coronoid process. The degree of synovitis was correlated with the degree of cartilage damage, but this correlation was weak or moderate, and overall the degree of inflammation of the synovium was mild, even in cases with hyaline cartilage ulceration. The presence of intra-articular osteochondral fragments in the elbow joint in cats is consistent with synovial osteochondromatosis secondary to DJD. Articular cartilage erosion is more severe in the medial compartment of the joint (medial coronoid process of the ulna and medial epicondyle of the humerus), for which no explanation has been identified. The lack of synovial inflammation even in cases with severe cartilage erosion could explain the previously reported absence of pain on manipulation of joints with radiographic signs of DJD in some cats. In addition, the presence of pain on manipulation of joints with DJD may not be explained by synovitis.

To our knowledge, this is the first report of macroscopic and histologic lesions of the elbow joint in cats, and even though our study was not designed to look at the prevalence of elbow DJD, we know from previous studies that feline elbow DJD is a condition that can be seen radiographically in 41% of cases. We believe this is an underestimation of the prevalence of this disease since most lesions of the cartilage seen grossly and histologically are grades 1 and 2 (mild/moderate), which will not be seen radiographically unless other degenerative changes are present in the joint, such as osteophytes. The most severe macroscopic as well as histological lesions of the articular surfaces were identified within the medial compartment of the elbow joint, and they occur without evidence of primary inflammatory disease, OCD, or FMCP. Cartilage damage ranged from superficial fibrillation to complete ulceration, and in the most severe cases, subchondral bone lesions such as cartilage islands and fibrovascular granulation tissue filling bone marrow spaces were identified. The degree of inflammation of the synovium was mild, even in cases with hyaline cartilage ulceration, and correlation with the degree of cartilage erosion was weak to moderate. Intra-articular osteochondral fragments found within the elbow joint were most consistent with synovial osteochondromatosis secondary to DJD. This is a common degenerative disease of the elbow joint in cats that has been overlooked, and the etiology is unknown.

Acknowledgements

We gratefully acknowledge the competent assistance of Mrs Monica Mattmuller of the Histology Laboratory of the Veterinary College of North Carolina State University for the preparation of the histological sections and special stains.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Comparative Pain Research Laboratory at North Carolina State University and a grant from Novartis Animal Health (Global Fellowship Program). Mila Freire was receiving salary support from Morris Animal Foundation during the preparation of this manuscript.

Supplemental Material

The online supplemental tables and figures are available at http://vet.sagepub.com/supplemental

References

1. Aeffner F, Weeren R, Morrison S, et al. Synovial osteochondromatosis with malignant transformation to chondrosarcoma in a dog. *Vet Pathol*. 2012;**49**:1036–1039.
2. Bennett D, Zainal Ariffin SM, Johnston P. Osteoarthritis in the cat, 1: how common is it and how easy to recognise? *J Feline Med Surg*. 2012;**14**:65–75.
3. Breit S, Pfeiffer K, Pichler R. Use of a 3D laser scan technique to compare the surface geometry of the medial coronoid process in dogs affected with medial compartment disease with unaffected controls. *Vet J*. 2010;**185**:285–291.
4. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study of 28 cases. *J Small Anim Pract*. 2006;**47**:439–445.
5. Clarke SP, Mellor D, Clements DN, et al. Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. *Vet Rec*. 2005;**157**:793–799.
6. Danielson KC, Fitzpatrick N, Muir P, et al. Histomorphometry of fragmented medial coronoid process in dogs: a comparison of affected and normal coronoid processes. *Vet Surg*. 2006;**35**:501–509.
7. Diaz-Bertrana C, Durall I, Rial JM, et al. Extra- and intra-articular synovial chondromatosis and malignant transformation to chondrosarcoma. *Vet Comp Orthop Traumatol*. 2010;**23**:277–283.
8. Edinger DT, Manley PA. Arthrodesis of the shoulder for synovial osteochondromatosis. *J Small Anim Pract*. 1998;**39**:397–400.

9. Fitzpatrick N, Yeadon R. Working algorithm for treatment decision making for developmental disease of the medial compartment of the elbow in dogs. *Vet Surg*. 2009;**38**:285–300.
10. Flo GL, Stickle RL, Dunstan RW. Synovial chondrometaplasia in five dogs. *J Am Vet Med Assoc*. 1987;**191**:1417–1422.
11. Freire M, Robertson I, Bondell HD, et al. Radiographic evaluation of feline appendicular degenerative joint disease vs. macroscopic appearance of articular cartilage. *Vet Radiol Ultrasound*. 2011;**52**: 239–247.
12. Godfrey DR. Osteoarthritis in cats: a retrospective radiological study. *J Small Anim Pract*. 2005;**46**:425–429.
13. Goldhammer MA, Smith SH, Fitzpatrick N, et al. A comparison of radiographic, arthroscopic and histological measures of articular pathology in the canine elbow joint. *Vet J*. 2010;**186**:96–103.
14. Gregory SP, Pearson GR. Synovial osteochondromatosis in a Labrador Retriever bitch. *J Small Anim Pract*. 1990;**31**:580–583.
15. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). *J Am Vet Med Assoc*. 2002;**220**:628–632.
16. Hubler M, Johnson K, Burling D, et al. Lesions resembling osteochondromatosis in two cats. *J Small Anim Pract*. 1986;**27**:181–187.
17. Krenn V, Morawietz L, Burmester GR, et al. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. *Histopathology*. 2006;**49**:358–364.
18. Lascelles BD. Feline degenerative joint disease. *Vet Surg*. 2010; **39**:2–13.
19. Lascelles BD, Henry JB III, Brown J, et al. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Vet Surg*. 2010;**39**:535–544.
20. Lavrijsen IC, Heuven HC, Voorhout G, et al. Phenotypic and genetic evaluation of elbow dysplasia in Dutch Labrador Retrievers, *Golden Retrievers, and Bernese Mountain dogs.* Vet J. 2012;**193**:486–492.
21. Mankin HJ, Dorfman H, Lippiello L, et al. Biochemical and metabolic abnormalities in articular cartilage from osteo-arthritic human hips, II: correlation of morphology with biochemical and metabolic data. *J Bone Joint Surg Am*. 1971;**53**:523–537.
22. McKenzie G, Raby N, Ritchie D. A pictorial review of primary synovial osteochondromatosis. *Eur Radiol*. 2008;**18**:2662–2669.
23. Meachim G. Light microscopy of Indian ink preparations of fibrillated cartilage. *Ann Rheum Dis*. 1972;**31**:457–464.
24. Moores AP, Benigni L, Lamb CR. Computed tomography versus arthroscopy for detection of canine elbow dysplasia lesions. *Vet Surg*. 2008;**37**:390–398.
25. Murphey MD, Vidal JA, Fanburg-Smith JC, et al. Imaging of synovial chondromatosis with radiologic-pathologic correlation. *Radiographics*. 2007;**27**:1465–1488.
26. Pritzker KP, Gay S, Jimenez SA, et al. Osteoarthritis cartilage histopathology: grading and staging. *Osteoarthritis Cartilage*. 2006; **14**:13–29.
27. Raya JG, Melkus G, Adam-Neumair S, et al. Diffusion-tensor imaging of human articular cartilage specimens with early signs of cartilage damage. *Radiology*. 2013;**266**:831–841.
28. Ryan JM, Lascelles BD, Benito J, et al. Histological and molecular characterisation of feline humeral condylar osteoarthritis. *BMC Vet Res*. 2013;**9**:110.
29. Slingerland LI, Hazewinkel HA, Meij BP, et al. Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. *Vet J*. 2011;**187**:304–309.
30. Smith TJ, Baltzer WI, Lohr C, et al. Primary synovial osteochondromatosis of the stifle in an English Mastiff. *Vet Comp Orthop Traumatol*. 2012;**25**:160–166.
31. Staiger BA, Beale BS. Use of arthroscopy for debridement of the elbow joint in cats. *J Am Vet Med Assoc*. 2005;**226**:401–403.
32. Tas O, De Cock H, Lemmens P, et al. Synovial osteochondromatosis and sclerosing osteosarcoma in a cat. *Vet Comp Orthop Traumatol*. 2013;**26**:160–164.
33. Yoshioka M, Coutts RD, Amiel D, et al. Characterization of a model of osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage*. 1996;**4**:87–98.

SUPPLEMENTAL MATERIAL

Figure S1: Ulna; cat. Normal articular cartilage. Hyaline articular cartilage is divided into superficial, mid and deep zones and it is separated from the calcified cartilage zone by the tidemark. HC= Hyaline cartilage; CCZ= Calcified cartilage zone; SB= subchondral bone. Hematoxylin-Eosin (HE) on the left, Safranin-O (SO) on the right.

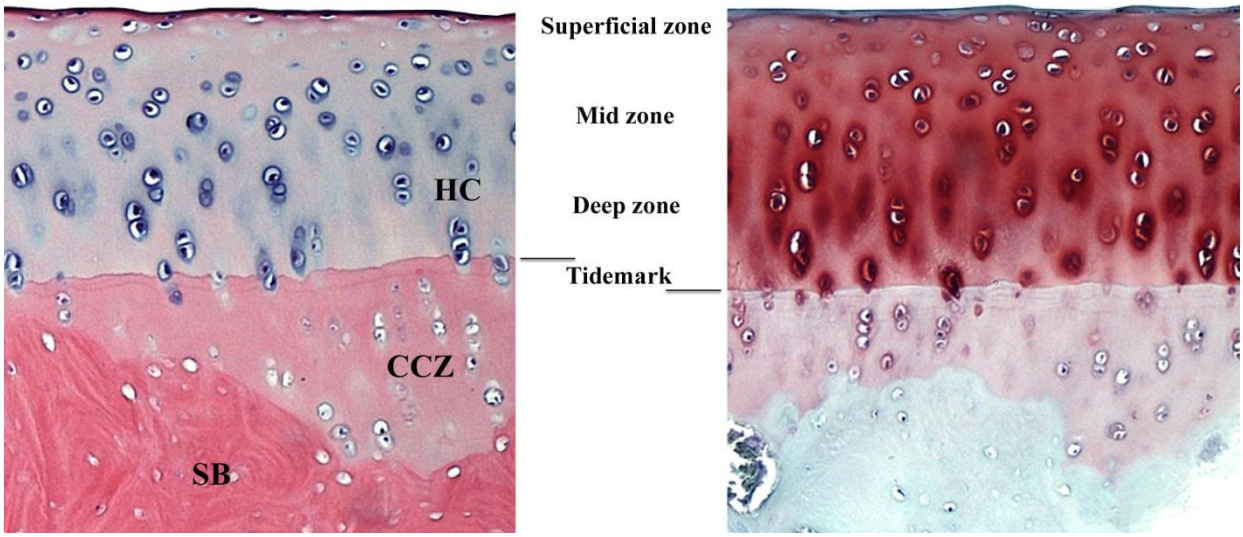

Table S1 – Microscopic Cartilage Damage grading system – Modification of the OARSI and Mankin histological and histochemical scoring Systems.

1. Structure Cartilage	Score
Normal	0
Superficial irregularities	1
Clefts to mid zone	2
Clefts to deep zone	3
Clefts to tidemark	4
Exposure of subchondral bone	5
2. Tidemark	
Normal	0
Crossed by blood vessels or double tidemark	1
3. Chondrocytes	
Normal density and organization	0
Decreased density and disorganized	1
4. Safranin-O staining	
Normal	0
Slight reduction superficially	1
Moderate reduction	2
Severe reduction	3
No stain	4
5. Cartilage islands in subchondral bone	
Absent	0
Mild	1
Moderate	2
Severe	3
6. Woven bone	
Normal	0
Increased and/or abnormal distribution mild	1
Increased and/or abnormal distribution moderate	2
Increased and/or abnormal distribution severe	3

Table S2. Histopathological assessment of the three features of chronic synovitis (Krenn *et al*. 2006).

A. Enlargement of the synovial lining cell layer	
0 points	The lining cells form one layer
1 point	The lining cells form 2-3 layers
2 points	The lining cells form 4-5 layes, few multinucleated cells might occur
3 points	The lining cells form more than 5 layers, the lining might be ulcerated and multinucleated cells might occur
B. Density of resident cells	
0 points	The synovial stroma shows normal cellularity
1 point	The cellularity is slightly increased
2 points	The cellularity is moderately increased, multinucleated cells might occur
3 points	The cellularity is greatly increased, multinucleated giant cells, pannus formation and rheumatoid granulomas might occur
C. Inflammatory infiltrate	
0 points	No inflammatory infiltrate
1 point	Few mostly perivascular situated lymphocytes or plasma cells
2 points	Numerous lymphocytes or plasma cells, sometimes forming follicle-like aggregates
3 points	Dense band-like inflammatory infiltrate or numerous large follicle-like aggregates
D. Final score interpretation	
Sum 0 or 1	No synovitis
Sum 2-4	Low-grade synovitis
Sum 5-9	High grade synovitis

Discussion

The studies described here have been able to confirm that the prevalence of DJD is high in domestic cats as it had been previously published.[1, 2, 5-8] It is possible that the population we used in the cross-sectional study for determination of the prevalence of radiographic signs of DJD, have introduced some bias because these animals were selected from a single feline-only veterinary practice and bias such as life-style, feeding and veterinary care may have been introduced in these cats, compared to the broader cat population as a whole. Soon after our work[14] was published, another cross-sectional study by Slingerland *et al.*[33] described the prevalence and clinical features of a population of 100 cats. Although these two works were designed differently, since the work by Slingerland evaluated only animals older than 6 years of age, they also found a high prevalence of radiographic signs of DJD (61% of animals had DJD in at least one joint) and a strong correlation of the presence of DJD with age. One of the questions that remained open after we determined the high prevalence of this disease was the clinical significance of this condition in cats. Slingerland *et al.*[33] studied the clinical signs shown by animals affected with this condition and suggested that lameness does not seem to be a clinical sign in a large population of cats. Instead, behavioral changes are the most common sign of pain in cats.

We spent considerable time precisely defining what features were to be classified as indicative of DJD in the appendicular joints in cats for grading of the radiographs evaluated in our studies. At the time of publication of the study of prevalence of the radiographic signs of DJD in feline species, very little information on the association between radiographic signs and gross or histological features of DJD in feline joints was available, so information used was mostly changes that are identified in joint degeneration of other species. However, we found that several radiographic features not normally observed in canine patients (such as medial meniscal

mineralization and periarticular mineralizations) were seen commonly in these cats. It could be argued that the inclusion of such features as indicative of DJD is erroneous because it was not proven to be secondary to joint degeneration or part of the degenerative process (for example, dorsal new bone on the intertarsal and tarsometatarsal joints), and other studies have suggested that periarticular soft tissue mineralizations may not represent DJD.[8] However we decided to include them on the basis of other work we have performed that demonstrated an association between those features and DJD as measured by cartilage damage.[34, 35] For example, our study of meniscal mineralization in domestic cats we observed that joints with meniscal mineralization and no other features of DJD, predictably had cartilage erosion and so the decision made was to include that radiographic finding as a sign of DJD in the stifle joint. Other poorly defined radiographic features, such as joint-associated mineralizations, may also be associated with joint degeneration. With respect to the axial skeleton, although it appears that investigators are describing the same general findings for axial skeleton DJD, the nomenclature used varies, as do the features included as being indicative of axial DJD.[5, 7-9, 36] This problem has recently been discussed,[37] and it is apparent that evaluation of the association between the radiographic findings in the axial skeleton and their association with macroscopic findings, as we did for the appendicular joints, needs to be performed for a better understanding of what the radiographic features commonly found in the axial skeleton corresponds to macroscopically. This will likely allow for revision and unification of the nomenclature used for describing those lesions.

The very high prevalence of appendicular skeleton DJD and the association between appendicular and axial skeleton DJD and age that we described is supported by previous and recent reports.[5, 8, 9, 12, 33, 38] Overall despite the high prevalence of radiographic DJD, the severity scores were relatively low and although this may reflect the particular population studied, it

might be that the radiographic severity of DJD in cats is less than in dogs as it has been suggested in previous studies.[8, 9] This needs further investigation.

Because of the different radiographic appearance of DJD in cats compared with dogs, we evaluated which radiographic findings were most commonly present in the different appendicular joints in cats and found that the most common radiographic features of DJD were joint-associated mineralizations for the elbow joint, tarsometatarsal dorsal bone proliferation, intraarticular mineralizations in the stifle joint and osteophytes in the coxofemoral joint. Except for the coxofemoral joint, osteophytes were not the most common radiographic sign of DJD, and this an important feature to emphasize because although the radiographic findings vary according to the stage of the disease, it is generally accepted that periarticular osteophyte formation of different degrees of severity are present in any joint affected with DJD. Since other forms of new bone formation and joint-associated and intra-articular mineralizations were seen commonly in feline joint with DJD, the sentiment that cats form less new bone in association with DJD than other species should be clarified. Based on our results, cats form periarticular new bone, but the radiographic appearance is different to dogs. The fact that some radiographic features not commonly seen in dogs, such as joint-associated mineralizations and meniscal mineralizations, were seen commonly in cats, suggests that the radiographic signs of DJD are different in cats than dogs. This needs further clarification.

The presence of cartilage damage in joints without any radiographic changes indicative of the presence of DJD is not surprising since it is well known that imaging of cartilage using radiography is impossible. Cartilage damage is an early change in the process of joint degeneration and other changes, such as osteophytosis and subchondral sclerosis, become apparent radiographically only in more advanced stages of the disease. However, based on what

we observed, severe cartilage damage with exposure of subchondral bone may be present with only mild radiographic evidence of DJD, and the prevalence of cartilage lesions in radiographically normal joints was high in some of the joints evaluated in our study. Clinically this might result in considering joints as normal when in reality their cartilage is damaged, or considering that the degree of degenerative disease is mild when severe cartilage damage is already present. Implementation of joint evaluation by imaging systems that better determine the state of articular cartilage would allow identification of joint degeneration more accurately and in early stages. Different degrees of cartilage damage can be detected using diffraction enhanced radiographic imaging,[39, 40] but this imaging modality is not readily available for veterinary practitioners, even in referral centers. Since conventional radiographs are the easiest indirect and most used method to evaluate degenerative changes in joints, we evaluated the usefulness of the radiographic features of osteoarthritis as predictors of articular cartilage degeneration, the same way that has been described in humans that marginal osteophytes are the most sensitive radiographic features for detection of osteoarthritis of the tibiofemoral joint.[41] Our results indicate that when considering all the joints, there is statistically significant correlation between cartilage damage and the detection of osteophytes and joint associated mineralizations, however this correlation was only fair. When looking at various joints individually, although most correlations were statistically significant, only the presence of osteophytes and the subjective radiographic DJD score had a moderate degree of correlation with the presence of cartilage damage for the elbow and coxofemoral joints. The other correlations evaluated were either only fair, or not significant as a result of the high number of joints with no radiographic signs of DJD but with cartilage lesions present. It can be deduced that radiographic signs of DJD in feline appendicular joints are not sensitive features for detection of DJD.

Trying to explain the etiological aspects of the presence of DJD in different appendicular joints and because of the high prevalence of radiographic evidence of meniscal mineralization we decided to investigate the pathological aspects associated with the presence of these mineralizations in the stifle joints in cats. Meniscal mineralization is a poorly understood condition that has been reported in many species including large non-domestic cats such as African lions, Bengal and Bengal-cross tigers.[16-19, 42] The cause of these mineralizations is unknown although one theory (phylogenetic theory) suggests that they represent a congenital vestigial structure that should be interpreted as a variant of normal anatomy.[21, 22] In our study meniscal mineralization was not only correlated with the degree of cartilage damage present in the joint, but in the case with the largest meniscal mineralization the cartilage lesion of the medial femoral condyle had form a distinct groove that appeared to articulate with the mineralization. A previous study also reported the presence of a groove in the medial femoral condyle that articulated with an ossicle of the medial meniscus in the stifle joint of a tiger (*Pantera tigris*)[17], and the authors suggested that the ossicles within the medial meniscus were a normal adaptive anatomic feature that helped distribution of load through the meniscus thereby reducing the wear and fatigue of the articular surfaces of the femur and tibia. In contrast to this, and based on our findings and the degree of damage present in the joints with meniscal mineralization, we consider the changes in the medial femoral condyle to be degenerative, likely in response, at least in part, to the presence of the meniscal mineralization.

Although we were able to show a clear relationship between meniscal mineralization and the presence of cartilage damage and the medial femoral condyle and medial tibial plateau, we still do not know if the meniscal mineralization is a cause or a result of the cartilage damage. The fact that there was more cartilage damage on the medial tibial plateau compared with the lateral

tibial plateau in the normal stifle might suggest that meniscal mineralization is a response to degenerative changes in this joint. Our results also suggest that meniscal mineralization may be associated with medial compartment joint disease of the stifle joint in cats, since cartilage lesions concentrated in the medial femoral condyle and medial aspect of the tibial plateau. In people, medial compartment DJD of the knee has been associated with high adduction moment at the knee during ambulation.[43-47] It may be that gait patterns, alteration of gait patterns, or pelvic limb conformation in some cats may predispose to meniscal mineralization, and this may in turn hasten the progression of DJD. This of course is speculative, but further investigation of the condition in cats may help in preventing the disease in this species.

The cause of meniscal mineralization is still debated. Our histologic findings seem to suggest that menisci undergo a process of ossification, starting with a chondro-osseus transformation of the fibrocartilage with mineral deposition, ultimately organizing into cancellous bone and bone marrow structure. That the ossified areas continue to grow by conversion of fibrocartilage to bone is suggested by the presence of chondro-osseus metaplasia of the fibrocartilage observed in the periphery of the ossified area. The bilateral symmetrical appearance of the meniscal mineralizations could support a nondegenerative origin, however, repetitive microtrauma because of bilateral gait abnormalities, or pelvic limb conformation in some cats could trigger the degenerative transformation at specific areas of the menisci bilaterally. In people, chondrocalcinosis of the meniscus has been associated with several distinct metabolic disorders including hemochroatosis, hyperparathyroidism and hypothyroidism.[48] The association between metabolic disorders and mineralization of menisci in cats is unknown.

Another joint in which we focused out attention is the elbow joint which has consistently been reported as the joint with the more severe radiographic signs of DJD and as being most commonly affected by this condition.[14, 15] When we performed the study of evaluation of radiographic signs indicative of DJD in cats and its association with macroscopic appearance of articular cartilage,[35] it became apparent that cartilage damage in this joint was located in the medial compartment, specifically in the articular surface of the medial coronoid process and medial aspect of the humeral condyle. Medial compartment elbow joint disease is recognized in dogs[49, 50] and is associated with medial coronoid process disease, humeroulnar incongruency and abnormal forces acting in the medial compartment of the joint,[51-53] but the cause of cartilage damage in the medial compartment of the elbow joints in cats was unknown. Further evaluation of the histopathological characteristics of the articular cartilage and synovium of the elbow joints in cats[54] did not reveal any of the features that are reported in dogs with fragmented coronoid process (microcracks in the subchondral bone, increased porosity and loss of osteocytes).[55, 56] We did not perform histomorphometry to evaluate bone or osteocyte density, however these changes were only seen in the areas of microcracks of the subchondral bone in dogs, and microcracks were not present in our specimens. It is possible that fissures may have been missed during processing of the samples for histopathological evaluation. Nevertheless, since no evidence of fragmented medial coronoid process or a histologic reaction to an adjacent microfracture was present in any of the specimens and fissuring or fracture of the coronoid process was not seen during macroscopic evaluation of any of the joints, we concluded that fragmentation of the coronoid process is not part of the pathogenesis of feline elbow DJD in the cases we evaluated. Some of the changes observed in the subchondral bone in the samples evaluated in our study were similar to those described in the subchondral bone of the medial coronoid process from

dogs with fragmented medial coronoid process (cartilage islands and fibrosis of the bone marrow spaces)[56], but these lesions are nonspecific responses of bone to a variety of insults and are not unique to coronoid disease. The cartilage islands within the subchondral bone observed in our specimens were likely consequence of the degree of cartilage degradation rather than pathology originating in the subchondral bone that leads to medial coronoid fragmentation.

The cause of elbow DJD in cats with this pattern of medial compartmentalization is still unknown. One of the theories proposed for the pathogenesis of fragmented coronoid process in dogs is the presence of abnormal loading forces in the elbow joint resulting from asymmetric growth of the radius and the ulna which causes increase loads in the coronoid process and subsequent fragmentation. Perhaps the same theory could explain why the lesions are concentrated in the medial compartment of the elbow joints in cats. In this case, further investigation will be necessary to elucidate why fragmentation of the medial coronoid process does not happen as a result of these theoretical abnormal loadings in feline species.

Histopathological characteristics of the free intra-articular osteochondral fragments and changes observed in the synovial stroma in the elbow joints seem to indicate that those fragments originate from the synovial membrane and therefore are consistent with synovial osteochondromatosis secondary to degenerative joint disease. Mention of feline synovial chondromatosis in the literature is scarce and in some cases the intra-articular fragments were referred to as “osteochondromas” although macroscopic and histopathological characteristics are consistent with our findings.[57, 58]

Evaluation of the synovial membrane in the elbow joints from cats with and without DJD revealed that severe synovial inflammation was not seen in any of the samples evaluated and

overall there was only mild inflammation in the synovium and very little synovial lining hyperplasia even in those elbow joints in which the articular cartilage was ulcerated. This suggests that the elbow lesions in our cases were not primary inflammatory in origin. Low synovitis scores have also been reported in dogs with different degrees of cartilage fibrillation secondary to fragmented coronoid process[56], and these results are consistent with Krenn *et al*.[59] where the mean synovitis score of human patients diagnosed with osteoarthritis was only 2 (range 0-6). It was not surprising to not see ulceration of the epithelial lining of the synovial membrane or severe inflammatory infiltrate of the synovial stroma since these features seem to correspond only with reactive or rheumatoid arthritis. It was not known if the animals included in our study were painful to manipulation of those joints, but if those joints were painful, the source of pain may be coming from a source other than the synovial membrane, since synovitis does not seem to be a consistent feature in feline elbow DJD.

We believe our studies have contributed to improve the understanding of the radiological and histopathological characteristics of feline appendicular degenerative joint disease. Important and common radiological features found in feline joints such as meniscal mineralization have been found to correlate with severe cartilage damage in some cases and very well known causes of elbow DJD in dogs that were mentioned as possible causes of feline elbow DJD have been ruled out to be present in these species. Many questions still remain without answer and further studies are necessary to elucidate more aspects of the etiology and clinical significance of this disease in domestic cats.

Conclusions

1. Ninety-one percent of domestic cats have at least 1 appendicular joint with radiographic signs of DJD and fifty-five percent of domesticated cats have radiographic signs of DJD in the axial skeleton. Overall, 92% of domestic cats have radiographic evidence of DJD somewhere in the skeleton.

2. The appendicular joints and spinal segment most frequently affected by radiographic signs of DJD are the hip, followed by the stifle, tarsus and elbow joints, and the thoracic segment respectively.

3. The appendicular joint with the most severe radiographic signs of DJD is the elbow joint and the spinal segment with the most severe radiographic signs of DJD is the lumbosacral region.

4. There is no evidence of association between DJD scores and the variables sex, percent of time spent indoors/outdoors, vaccination status (rabies, FeLV, FVRCP), use of flea/tick preventatives and FeLV or FIV status. However there is overwhelming evidence that the total DJD radiographic score changes with the age of the cat.

5. Digital radiographs are equally or more sensitive for detection of articular degenerative changes when compared with analog radiographs.

6. The most common radiographic features indicative of DJD are joint-associated mineralizations for the elbow joint, tarso-metatarsal dorsal bone proliferation in the tarsal

joint, intra-articular mineralizations in the stifle joint and osteophytes in the coxofemoral joint.

7. The joint most likely to have cartilage damage without radiographic evidence of DJD is the stifle followed by the coxofemoral joint, elbow and tarsal joint.

8. The digital radiographic finding indicative of DJD with the greatest association with cartilage damage is the presence of osteophytes for the elbow, tarsal and coxofemoral joints, and intra-articular mineralizations for the stifle joint.

9. Forty-six percent of domesticated cats have radiographic signs consistent with meniscal mineralization in one or both stifle joints.

10. Meniscal mineralization in domestic cats is bilaterally symmetrical, located in the cranial horn of the medial meniscus and can present as a single area or multiple areas of mineralizations.

11. The severity of the radiographic signs indicative of DJD and severity of macroscopic cartilage damage in the stifle joints of domestic cats are significantly higher for stifles with meniscal mineralization compared with stifles without meniscal mineralization.

12. Presence of meniscal mineralization in domesticated cats is associated with medial compartment joint disease of the stifle joint as indicated by the presence of cartilage damage on the medial femoral condyle and medial tibial condyle.

13. The appendicular joint with the greatest extent of macroscopic cartilage damage is the elbow joint. This joint is followed by the stifle, coxofemoral and tarsal joints.

14. Macroscopic and histological evaluation of the articular cartilage of the elbow joint in domesticated cats indicates the presence of medial compartment joint disease for which a cause has not been identified.

15. Feline elbow joints evaluated with radiographic signs of DJD, articular cartilage damage and intra-articular osteochondral fragments do not have macroscopic or histological evidence of presence of fragmented medial coronoid process.

16. The presence of intra-articular osteochondral fragments in the elbow joints of domestic cats is consistent with synovial osteochondromatosis secondary to degenerative joint disease.

References

1. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994-1997). *Journal of the American Veterinary Medical Association*. 2002;220: 628-632.

2. Godfrey DR. Osteoarthritis in cats: a retrospective radiological study. *Journal of Small Animal Practice*. 2005;46: 425-429.

3. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study of 28 cases. *Journal of Small Animal Practice*. 2006;47: 439-445.

4. Clarke SP, Mellor D, Clements DN, Gemmill T, Farrell M, Carmichael S, et *al*. Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. *The Veterinary Record*. 2005;157: 793-799.

5. Beadman R SR, King AS. Vertebral osteophytes in the cat. *The Veterinary Record*. 1964;76: 1005-1007.

6. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study of 28 cases. *Journal of Small Animimal Practice*. 2006;47: 439-445.

7. Lascelles BD, Hansen BD, Roe S, DePuy V, Thomson A, Pierce CC, et *al*. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *Journal of Veterinary Internal Medicine*. 2007;21: 410-416.

8. Clarke SP, Mellor D, Clements DN, Gemmill T, Farrell M, Carmichael S, et *al*. Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. *The Veterinary Record*. 2005;157: 793-799.

9. Hardie EM, Roe SC, Martin FR. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994-1997). *Journal of the American Veterinary Medical Association*. 2002;220: 628-632.

10. Langenbach A, Green P, Giger U, Rhodes H, Gregor TP, LaFond E, et *al*. Relationship between degenerative joint disease and hip joint laxity by use of distraction index and Norberg angle measurement in a group of cats. *Journal of the American Veterinary Medical Association*. 1998;213: 1439-1443.

11. Keller GG, Reed AL, Lattimer JC, Corley EA. Hip dysplasia: a feline population study. *Veterinary Radiology & Ultrasound*. 1999;40: 460-464.

12. Godfrey DR. Osteoarthritis in cats: a retrospective radiological study. *Journal of Small Animal Practice*. 2005;46: 425-429.

13. Allan GS. Radiographic features of feline joint diseases. *Veterinary Clinics of North America: Small Animal Practice*. 2000;30: 281-302, vi.

14. Lascelles BD, Henry JB, 3rd, Brown J, Robertson I, Sumrell AT, Simpson W, et *al*. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Veterinary Surgery*. 2010;39: 535-544.

15. Slingerland LI, Hazewinkel HA, Meij BP, Picavet P, Voorhout G. Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. *The Veterinary Journal*. 2011;187: 304-309.

16. Whiting PG, Pool RR. Intrameniscal Calcification and Ossification in the Stifle Joints of Three Domestic Cats. *Journal of the American Animal Hospital Association*. 1985;21: 579-584.

17. Ganey TM, Ogden JA, Abou-Madi N, Colville B, Zdyziarski JM, Olsen JH. Meniscal ossification. II. The normal pattern in the tiger knee. *Skeletal Radiology*. 1994;23: 173-179.

18. Kirberger RM, Groenewald HB, Wagner WM. A radiological study of the sesamoid bones and os meniscus of the cheetah (Acinonyx jabatus). *Veterinary and Comparative Orthopaedics and Traumatology*. 2000;13: 172-177.

19. Pedersen HE. The ossicles of the semilunar cartilages of rodents. *The Anatomical Record*. 1949;105: 1-9.

20. Noble J, Hamblen DL. The pathology of the degenerate meniscus lesion. *The Journal of Bone and Joint Surgery*. 1975;57: 180-186.

21. Rosen IE. Unusual intrameniscal lunulae; three case reports *The Journal of Bone and Joint Surgery*. 1958;40-A: 925-928.

22. Liu SH, Osti L, Raskin A, Merlo F, Bocchi L. Meniscal ossicles: two case reports and a review of the literature. *Arthroscopy*. 1994;10: 296-298.

23. Yoo JH, Yang BK, Son BK. Meniscal ossicle: a case report. *Knee*. 2007;14: 493-496.

24. Schaefer WD, Martin DF, Pope TL, Jr, Rudicil HS. Meniscal ossicle. *Journal of the Southern Orthopedic Association*. 1996;5: 126-129.

25. Schnarkowski P, Tirman PF, Fuchigami KD, Crues JV, Butler MG, Genant HK. Meniscal ossicle: radiographic and MR imaging findings. *Radiology*. 1995;196: 47-50.

26. Kato Y, Oshida M, Saito A, Ryu J. Meniscal ossicles. *Journal of Orthopedic Science*. 2007;12: 375-380.

27. Ogden JA, Ganey TM, Arrington JA, Leffers D. Meniscal ossification. I. Human. *Skeletal Radiology*. 1994;23: 167-172.

28. Reinke J, Mughannam A. Meniscal Calcification and Ossification in Six Cats and Two Dogs. *Journal of the American Animal Hospital Association*. 1994;30: 145-152.

29. Weber NA. Apparent primary ossification of the menisci in a dog. *Journal of the American Veterinary Medical Association*. 1998;212: 1892-1894.

30. Lascelles BD, Henry JB, Brown J, Thomson A, Simpson W, Hansen BD, et *al*. Cross-sectional study evaluating the prevalence of radiographic degenerative joint disease in domesticated cats. *Veterinary Surgery*. 2010; 3(5):535-44.

31. Lavrijsen IC, Heuven HC, Voorhout G, Meij BP, Theyse LF, Leegwater PA, et *al*. Phenotypic and genetic evaluation of elbow dysplasia in Dutch Labrador Retrievers, Golden Retrievers, and Bernese Mountain dogs. *The Veterinary Journal*. 2012;193: 486-492.

32. Staiger BA, Beale BS. Use of arthroscopy for debridement of the elbow joint in cats. *Journal of the American Veterinary Medical Association*. 2005;226: 401-403, 376.

33. Slingerland LI, Hazewinkel HA, Meij BP, Picavet P, Voorhout G. Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. *The Veterinary Journal*. 2011;187: 304-309.

34. Freire M, Brown J, Robertson ID, Pease AP, Hash J, Hunter S, et *al*. Meniscal Mineralization in Domestic Cats. *Veterinary Surgery*. 2010.

35. Freire M, Robertson I, Bondell HD, Brown J, Hash J, Pease AP, et *al*. Radiographic evaluation of feline appendicular degenerative joint disease vs. Macroscopic appearance of articular cartilage. *Veterinary Radiology & Ultrasound*. 2011;52: 239-247.

36. Rothschild BM, Rothschild C, Woods RJ. Inflammatory arthritis in large cats: an expanded spectrum of spondyloarthropathy. *Journal of Zoo and Wildilife Medicine*. 1998;29: 279-284.

37. Lascelles BD. Feline degenerative joint disease. *Veterinary Surgery*. 2010;39: 2-13.

38. Pacchiana PD, Gilley RS, Wallace LJ, Hayden DW, Feeney DA, Jessen CR, et *al*. Absolute and relative cell counts for synovial fluid from clinically normal shoulder and stifle joints in cats. *Journal of the American Veterinary Medical Association*. 2004;225: 1866-1870.

39. Muehleman C, Li J, Zhong Z. Preliminary study on diffraction enhanced radiographic imaging for a canine model of cartilage damage. *Osteoarthritis and Cartilage*. 2006;14: 882-888.

40. Muehleman C, Chapman LD, Kuettner KE, Rieff J, Mollenhauer JA, Massuda K, et *al*. Radiography of rabbit articular cartilage with diffraction-enhanced imaging. *Anatomical Record part A*. 2003;272: 392-397.

41. Kijowski R, Blankenbaker D, Stanton P, Fine J, De Smet A. Correlation between radiographic findings of osteoarthritis and arthroscopic findings of articular cartilage degeneration within the patellofemoral joint. *Skeletal Radiology*. 2006;35: 895-902.

42. Walker M, Phalan D, Jensen J, Johnson J, Drew M, Samii V, et *al*. Meniscal ossicles in large non-domestic cats. *Veterinary Radiology & Ultrasound*. 2002;43: 249-254.

43. Hurwitz DE, Sumner DR, Andriacchi TP, Sugar DA. Dynamic knee loads during gait predict proximal tibial bone distribution. *Journal of Biomechanics*. 1998;31: 423-430.

44. Mundermann A, Asay JL, Mundermann L, Andriacchi TP. Implications of increased medio-lateral trunk sway for ambulatory mechanics. *Journal of Biomechanics*. 2008;41: 165-170.

45. Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW, Jr, Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *Journal of Orthopaedic Research*. 2007;25: 789-797.

46. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. *Gait & Posture*. 2007;26: 436-441.

47. Hunt MA, Birmingham TB, Bryant D, Jones I, Giffin JR, Jenkyn TR, et *al*. Lateral trunk lean explains variation in dynamic knee joint load in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage*. 2008;16: 591-599.

48. Hough AJ, Jr., Webber RJ. Pathology of the meniscus. *Clinical Orthopaedics and Related Research*. 1990: 32-40.

49. Fitzpatrick N, Yeadon R. Working algorithm for treatment decision making for developmental disease of the medial compartment of the elbow in dogs. *Veterinary Surgery*. 2009;38: 285-300.

50. Fitzpatrick N, Yeadon R, Smith T, Schulz K. Techniques of application and initial clinical experience with sliding humeral osteotomy for treatment of medial compartment disease of the canine elbow. *Veterinary Surgery*. 2009;38: 261-278.

51. Ness MG. Treatment of fragmented coronoid process in young dogs by proximal ulnar osteotomy. *Journal of Small Animal Practice*. 1998;39: 15-18.

52. Fitzpatrick N, Smith TJ, Evans RB, Yeadon R. Radiographic and arthroscopic findings in the elbow joints of 263 dogs with medial coronoid disease. *Veterinary Surgery*. 2009;38: 213-223.

53. Kirberger RM, Fourie SL. Elbow dysplasia in the dog: pathophysiology, diagnosis and control. *Journal of the South African Veterinary Association*. 1998;69: 43-54.

54. Freire M, Meuten D, Lascelles BDX. Pathology of articular cartilage and synovial membrane from elbow joints with and without degenerative joint diseas in domestic cats. *Veterinary Pathology*. 2014.

55. Danielson KC, Fitzpatrick N, Muir P, Manley PA. Histomorphometry of fragmented medial coronoid process in dogs: a comparison of affected and normal coronoid processes. *Veterinary Surgery*. 2006;35: 501-509.

56. Goldhammer MA, Smith SH, Fitzpatrick N, Clements DN. A comparison of radiographic, arthroscopic and histological measures of articular pathology in the canine elbow joint. *The Veterinary Journal*. 2010;186: 96-103.

57. Hubler M, Johnson K, Burling D, Ratcliffe R. Lesions Resembling Osteochondromatosis in two cats. *Journal of Small Animal Practice*. 1986;27: 181-187.

58. Bennett D, Zainal Ariffin SM, Johnston P. Osteoarthritis in the cat: 1. How common is it and how easy to recognise? *Journal of Feline Medicine and Surgery*. 2012;14: 65-75.

59. Krenn V, Morawietz L, Burmester GR, Kinne RW, Mueller-Ladner U, Muller B, et *al*. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. *Histopathology*. 2006;49: 358-364.